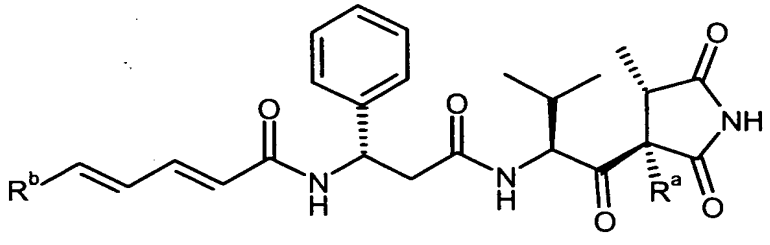
Arylamides

The present invention relates to compounds, to processes for preparing them, to pharmaceutical compositions comprising them, and to their use in the therapy and/or prophylaxis of diseases in people or animals, especially diseases of bacterial infection.

The natural substances moiramide B (R^a = hydrogen, R^b = methyl) and andrimid (R^a = hydrogen, R^b = propenyl) have been described as having antibacterial activity, whereas moiramide C (R^a = hydroxyl, R^b = propenyl) is inactive. (A. Fredenhagen, S. Y. Tamura, P. T. M. Kenny, H. Komura, Y. Naya, K. Nakanishi, *J. Am. Chem. Soc.*, 1987, 109, 4409-4411; J. Needham, M. T. Kelly, M. Ishige, R. J. Andersen, *J. Org. Chem.*, 1994, 59, 2058-2063; M. P. Singh, M. J. Mroczenski-Wildey, D. A. Steinberg, R. J. Andersen, W. M. Maiese, M. Greenstein, *J. Antibiot.*, 1997, 50(3), 270-273). The isolation and antibacterial activity of andrimid is also desccribed in EP-A-250 115. JP 01301657 describes the use of andrimid and certain amide-type derivatives as agrochemical antibiotics.

The synthesis of andrimid is described in A. V. Rama Rao, A. K. Singh, Ch. V. N. S. Varaprasad, *Tetrahedron Letters*, **1991**, *32*, 4393-4396, that of moiramide B and andrimid in S. G. Davies, D. J. Dixon, *J. Chem. Soc., Perkin Trans.* 1, 1998, 2635-2643.

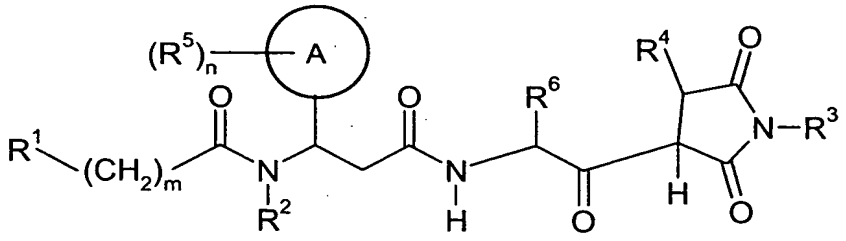


Although antibacterial products with different structures are on the market, a regular possibility is the development of resistance. New products for improved and effective therapy are therefore desirable.

It is an object of the present invention, therefore, to provide new and alternative compounds having equal or improved antibacterial action for treating bacterial diseases in people and animals.

Surprisingly it has been found that derivatives of this class of compound in which the beta-phenylalanine amide group is replaced by a heteroaromatic or substituted aromatic amide have antibacterial activity.

The present invention provides compounds of the formula



(I),

in which

R^1 is heteroaryl,

where heteroaryl can be substituted by 0, 1, 2 or 3 substituents R^{1-1}, the substituents R^{1-1} being selected independently of one another from the group consisting of halogen, alkyl, nitro, amino, alkylamino, cyano, trifluoromethyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, hydroxyl, alkoxy, aryloxy, benzyloxy, carboxyl, alkoxycarbonyl, aminocarbonyl, alkylcarbonylamino, alkylaminocarbonyl and aminosulfonyl,

or

R^1 is aryl,

where aryl is substituted by 1, 2 or 3 substituents R^{1-2}, the substituents R^{1-2} being selected independently of one another from the group consisting of halogen, alkyl, nitro, amino, alkylamino, cyano, trifluoromethyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, hydroxyl, alkoxy, aryloxy, benzyloxy, carboxyl, alkoxycarbonyl, aminocarbonyl, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonyl and aminosulfonyl,

or

two substituents R^{1-2}, together with the carbon atoms to which they are attached, form a cycloalkyl or heterocyclyl which can be substituted by 0, 1 or 2 substituents R^{1-2-1}, the substituents R^{1-2-1} being selected independently of one another from the group consisting of halogen, nitro, amino, trifluoromethyl, hydroxyl, alkyl and alkoxy,

R^2 is hydrogen or methyl,

R^3 is hydrogen, hydroxyl, amino, C_1–C_3 alkyl, benzyl, C_1–C_3 alkoxy, benzyloxy, C_1–C_3 alkylamino, C_1–C_3 alkylcarbonylamino, phenylcarbonylamino or benzylcarbonylamino,

R^4 is hydrogen or C_1–C_3 alkyl,

R^5 is halogen, trifluoromethyl, trifluoromethoxy, nitro, amino, alkylamino, hydroxyl, alkyl, alkoxy, carboxyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, aryl or heteroaryl,

or

two substituents R^5 together with the carbon atoms to which they are attached form a cycloalkyl or heterocyclyl each of which may be substituted by 0, 1 or 2 substituents R^{5-1}, the substituents R^{5-1} being selected independently of one another from the group consisting of halogen, nitro, amino, trifluoromethyl, hydroxyl, alkyl and alkoxy,

R^6 is alkyl, cycloalkyl, cycloalkenyl or heterocyclyl,

it being possible for R^6 to be substituted by 0, 1 or 2 substituents R^{6-1}, the substituents R^{6-1} being selected independently of one another from the group consisting of halogen, nitro, amino, trifluoromethyl, hydroxyl, alkyl and alkoxy,

n is a number 0, 1, 2 or 3,

it being possible for the radicals R^5 to be identical or different when n is 2 or 3,

m is a number 0, 1, 2, 3 or 4,

A is aryl or heteroaryl,

and their salts, their solvates and the solvates of their salts.

Compounds of the invention are the compounds of the formula (I) and their salts, solvates and solvates of the salts, the compounds of the formula (Ia), mentioned below, that are embraced by formula (I), and their salts, solvates and solvates of the salts, and also the compounds embraced by formula (I) and (Ia) and referred to below as implementation example(s), and their salts, solvates and solvates of the salts,

where the compounds referred to below and embraced by formula (I) and/or (Ia) are not already salts, solvates and solvates of the salts.

Depending on their structure the compounds of the invention may exist in stereoisomeric forms (enantiomers, diastereomers). The invention therefore relates to the enantiomers or diastereomers and their respective mixtures. From such mixtures of enantiomers and/or diastereomers it is possible to isolate the stereoisomerically uniform constituents in a known way.

The invention relates also, depending on the structure of the compounds, to tautomers of the compounds.

Salts preferred in the context of the invention are physiologically acceptable salts of the compounds of the invention.

Physiologically acceptable salts of the compounds (I) embrace acid addition salts of mineral acids, carboxylic acids and sulfonic acids, e.g., salts of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, benzenesulfonic acid, naphthalenedisulfonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid and benzoic acid.

Physiologically acceptable salts of the compounds (I) also embrace salts of customary bases, such as, by way of example and preferably, alkali metal salts (e.g., sodium and potassium salts), alkaline earth metal salts (e.g. calcium and magnesium salts) and ammonium salts derived from ammonia or organic amines having 1 to 16 carbon atoms, such as, by way of example and preferably, ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclo-hexylamine, dimethylaminoethanol, procaine, dibenzylamine, n-methylmorpholine, dihydroabietylamine, arginine, lysine, ethylenediamine and methylpiperidin.

Solvates in the context of the invention are those forms of the compounds which in the solid or liquid state form a complex by coordination with solvent molecules. Hydrates are one specific form of the solvates, in which the coordination is with water.

In the context of the present invention the signification of the substituents, unless specified otherwise, is as follows

Alkyl per se and "alk" and "alkyl" in alkoxy, alkylamino, alkylaminocarbonyl, alkylcarbonylamino and alkoxycarbonyl are a linear or branched alkyl radical having generally 1 to 8, preferably 1 to 6, more preferably 1 to 4, very preferably 1 to 3 carbon atoms, by way of example and preferably methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-pentyl and n-hexyl.

Alkoxy is by way of example and preferably methoxy, ethoxy, n-propoxy, isopropoxy, tert-butoxy, n-pentoxy and n-hexoxy.

Alkylamino is an alkylamino radical having one or two alkyl substituents (chosen independently of one another), the alkyl substituents independently of one another having generally 1 to 6, preferably 1 to 4, more preferably 1 to 3 carbon atoms, by way of example and preferably methylamino, ethylamino, n-propylamino, isopropylamino, tert-butylamino, n-pentylamino, n-hexylamino, *N,N*-dimethylamino, *N,N*-diethylamino, *N*-ethyl-*N*-methylamino, *N*-methyl-*N*-n-propylamino, *N*-isopropyl-*N*-n-propylamino, *N*-t-butyl-*N*-methylamino, *N*-ethyl-*N*-n-pentylamino and *N*-n-hexyl-*N*-methylamino. Thus C_1-C_3 alkylamino is for example a monoalkylamino radical having 1 to 3 carbon atoms or a dialkylamino radical having 1 to 3 carbon atoms in each alkyl substituent.

Alkylaminocarbonyl is an alkylaminocarbonyl radical having one or two alkyl substituents (chosen independently of one another), the alkyl substituents independently of one another having generally 1 to 6, preferably 1 to 4, more

preferably 1 to 3 carbon atoms, by way of example and preferably methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, isopropylaminocarbonyl, tert-butylaminocarbonyl, n-pentylaminocarbonyl, n-hexylaminocarbonyl, *N,N*-dimethylaminocarbonyl, *N,N*-diethylaminocarbonyl, *N*-ethyl-*N*-methylaminocarbonyl, *N*-methyl-*N*-n-propylaminocarbonyl, *N*-isopropyl-*N*-n-propylaminocarbonyl, *N*-t-butyl-*N*-methylaminocarbonyl, *N*-ethyl-*N*-n-pentylaminocarbonyl and *N*-n-hexyl-*N*-methylaminocarbonyl. C_1-C_3 alkylaminocarbonyl is for example a monoalkylaminocarbonyl radical having 1 to 3 carbon atoms or a dialkylaminocarbonyl radical having 1 to 3 carbon atoms in each alkyl substituent.

Alkylcarbonylamino is by way of example and preferably methylcarbonylamino, ethylcarbonylamino, n-propylcarbonylamino, isopropylcarbonylamino, tert-butylcarbonylamino, n-pentylcarbonylamino and n-hexylcarbonylamino.

Alkoxycarbonyl is by way of example and preferably methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, n-pentoxycarbonyl and n-hexoxycarbonyl.

Cycloalkyl is a cycloalkyl group having generally 3 to 8, preferably 5 to 7 carbon atoms; specified by way of example and preferably for cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. In the case of a cycloalkyl formed by two aryl substituents together with the aryl carbon atoms to which they are attached, two carbon atoms of the cycloalkyl group are sp^2 hybridized.

Cycloalkenyl is a cycloalkyl group having generally 3 to 8, preferably 5 to 7 carbon atoms; specified by way of example and preferably for cycloalkenyl are cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptenyl.

Aryl is a mono- to tricyclic aromatic radical having generally 6 to 14 carbon atoms; specified by way of example and preferably for aryl are phenyl, naphthyl and phenanthrenyl.

Aryloxy is a mono- to tricyclic aromatic radical, attached via an oxygen atom, and having generally 6 to 14 carbon atoms, by way of example and preferably phenoxy, naphthyloxy and phenanthrenyloxy.

Arylcarbonylamino is by way of example and preferably phenylcarbonylamino, naphthylcarbonylamino and phenanthrenylcarbonylamino.

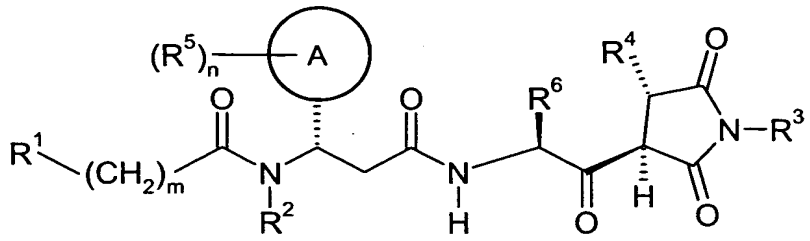
Heteroaryl is an aromatic, mono- or bicyclic radical having generally 5 to 10, preferably 5 to 6 ring atoms and up to 5, preferably up to 4, heteroatoms from the series S, O and N; by way of example and preferably thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, oxadiazolyl, pyrazolyl, imidazolyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, indolyl, indazolyl, benzofuranyl, benzothiophenyl, quinolinyl, isoquinolinyl.

Heterocyclyl is a mono- or polycyclic, preferably mono- or bicyclic, heterocyclic radical having generally 4 to 10, preferably 5 to 8 ring atoms and up to 3, preferably up to 2, heteroatoms and/or hetero-groups from the series N, O, S, SO, SO_2. The heterocyclyl radicals may be saturated or partly unsaturated. Preference is given to 5- to 8-membered, monocyclic saturated heterocyclyl radicals having up to two heteroatoms from the series O, N and S, such as, by way of example and preferably, tetrahydrofuran-2-yl, tetrahydrothienyl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolinyl, pyranyl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, thiopyranyl, morpholin-1-yl, morpholin-2-yl, morpholin-3-yl, perhydroazepinyl, piperazin-1-yl, piperazin-2-yl.

Halogen is fluorine, chlorine, bromine and iodine, preferably fluorine and chlorine.

If radicals in the compounds of the invention are substituted, the radicals, unless specified otherwise, may be substituted by one or more identical or different substituents. Substitution by up to three identical or different substituents is preferred. Very particular preference is given to substitution by one substituent.

Preference is given in the context of the present invention to compounds of the formula



(Ia)

in which R^1 to R^6, A, m and n are as defined for formula (I), and their salts, their solvates and the solvates of their salts.

Preference is given in the context of the present invention to compounds of the invention in which

R^1 is 5-, 6-, 9- or 10-membered heteroaryl,

where R^1 can be substituted by 0, 1 or 2 substituents R^{1-1}, the substituents R^{1-1} being selected independently of one another from the group consisting of halogen, alkyl, amino, alkylamino, cyano, trifluoromethyl, aryl, heteroaryl, alkoxy, alkoxycarbonyl and aminocarbonyl,

or

R^1 is phenyl or naphthyl,

where phenyl or naphthyl are substituted by 1, 2 or 3 substituents R^{1-2}, the substituents R^{1-2} being selected independently of one another from the group consisting of halogen, alkyl, nitro, amino, alkylamino, cyano, trifluoromethyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, aryloxy, benzyloxy,

alkoxycarbonyl, aminocarbonyl, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonyl and aminosulfonyl,

or

two substituents R^{1-2}, together with the carbon atoms to which they are attached, form a 5- or 6-membered cycloalkyl or a 5- or 6-membered heterocyclyl,

R^2 is hydrogen,

R^3 is hydrogen, hydroxyl, amino, methyl, benzyl, C_1-C_3 alkoxy, benzyloxy or C_1-C_3 alkylamino,

R^4 is methyl,

R^5 is fluoro, chloro, trifluoromethyl, trifluoromethoxy, nitro, amino, alkylamino, hydroxyl, alkoxy, aminocarbonyl, alkoxycarbonyl, alkyl, phenyl or 5- or 6-membered heteroaryl,

or

two substituents R^5, together with the carbon atoms to which they are attached, form a 5- or 6-membered cycloalkyl or 5- or 6-membered heterocyclyl,

R^6 is C_2-C_7 alkyl or 3- to 7-membered cycloalkyl,

where R^6 can be substituted by 0, 1 or 2 substituents R^{6-1}, the substituents R^{6-1} being selected independently of one another from the group consisting of halogen, alkoxy, alkyl and trifluoromethyl,

n is a number 0, 1 or 2,

where, if n is 2, the radicals R^5 can be identical or different,

m is a number 0, 1, 2 or 3,

and

A is phenyl, naphthyl or 5-, 6-, 9- or 10-membered heteroaryl.

Preference in the context of the present invention is also given to compounds of the invention in which

R^1 is pyridyl, imidazolyl, thienyl, furyl, oxadiazolyl, pyrazolyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinolinyl or isoquinolinyl,

where R^1 can be substituted by 0, 1 or 2 substituents R^{1-1}, the substituents R^{1-1} being selected independently of one another from the group consisting of halogen, alkyl, amino, trifluoromethyl, phenyl and alkoxy,

or

R^1 is phenyl or naphthyl,

where phenyl or naphthyl are substituted by 1, 2 or 3 substituents R^{1-2}, the substituents R^{1-2} being selected independently of one another from the group consisting of halogen, C_1-C_4 alkyl, dimethylamino, cyano, trifluoromethyl, 3- to 7-membered cycloalkyl, 5- or 6-membered heterocyclyl, phenyl, 5- or 6-membered heteroaryl, C_1-C_3 alkoxy, phenyloxy, benzyloxy, phenylcarbonylamino and aminosulfonyl,

or

two substituents R^{1-2}, together with the carbon atoms to which they are attached, form a 1,3-benzodioxole or a 1,4-benzodioxane,

R^2 is hydrogen,

R^3 is hydrogen, amino, methyl, methoxy, ethoxy, methylamino or dimethylamino,

R^4 is methyl,

R^5 is fluoro, chloro, trifluoromethyl, C_1-C_4 alkoxy, methoxycarbonyl, C_1-C_4 alkyl, phenyl or pyridyl,

or

two substituents R^5, together with the phenyl ring to which they are attached, form a 1,3-benzodioxole or a 1,4-benzodioxane,

R^6 is C_3–C_6 alkyl or 3- to 6-membered cycloalkyl,

n is a number 0, 1 or 2,

and, if n is 2, the radicals R^5 can be identical or different,

m is a number 0, 1, 2 or 3,

and

A is phenyl, naphthyl, pyridyl, thienyl, furanyl, quinolinyl or isoquinolinyl.

Preference in the context of the present invention is also given to compounds of the invention in which

R^1 is pyridyl, thienyl, furyl, quinolinyl or isoquinolinyl,

where R^1 can be substituted by 0, 1 or 2 substituents R^{1-1}, the substituents R^{1-1} being selected independently of one another from the group consisting of halogen, C_1-C_4 alkyl, trifluoromethyl, phenyl and C_1–C_3-alkoxy,

or

R^1 is phenyl or naphthyl,

where phenyl or naphthyl are substituted by 1, 2 or 3 substituents R^{1-2}, the substituents R^{1-2} being selected independently of one another from the group consisting of halogen, C_1-C_4 alkyl, dimethylamino, cyano, trifluoromethyl, 5- or 6-membered heterocyclyl, 5- or 6-membered heteroaryl, C_1-C_3 alkoxy, phenyloxy or benzyloxy,

or

two substituents R^{1-2}, together with the carbon atoms to which they are attached, form a 1,3-benzodioxole or a 1,4-benzodioxane,

R^2 is hydrogen,

R^3 is hydrogen, amino, methylamino or dimethylamino,

R^4 is methyl,

R^5 is fluoro, chloro, trifluoromethyl, C_1-C_3 alkoxy, C_1-C_4 alkyl, phenyl or pyridyl,

R^6 is isopropyl, tert-butyl, isopentyl, cyclopentyl or cyclohexyl,

n is a number 0, 1 or 2,

and, if n is 2, the radicals R^5 can be identical or different,

m is a number 0, 1 or 2,

and

A is phenyl, naphthyl, pyridyl, thienyl, quinolinyl or isoquinolinyl.

Preference in the context of the present invention is also given to compounds of the invention in which

R^1 is pyridyl, thienyl, furyl, quinolinyl or isoquinolinyl,

where R^1 can be substituted by 0, 1 or 2 substituents R^{1-1}, the substituents R^{1-1} being selected independently of one another from the group consisting of fluoro, chloro, trifluoromethyl, C_1-C_4 alkyl, phenyl and methoxy.

Preference in the context of the present invention is also given to compounds of the invention in which

R^1 is phenyl or naphthyl,

where phenyl or naphthyl are substituted by 1, 2 or 3 substituents R^{1-2}, the substituents R^{1-2} being selected independently of one another from the group consisting of halogen, C_1-C_4 alkyl, dimethylamino, cyano, trifluoromethyl, 5- or 6-membered heterocyclyl, 5- or 6-membered heteroaryl, C_1-C_3 alkoxy, phenyloxy or benzyloxy,

or

two substituents R^{1-2}, together with the carbon atoms to which they are attached, form a 1,3-benzodioxole or a 1,4-benzodioxane.

Preference in the context of the present invention is also given to compounds of the invention in which R^2 is hydrogen.

Preference in the context of the present invention is also given to compounds of the invention in which R^3 is hydrogen or amino.

Preference in the context of the present invention is also given to compounds of the invention in which R^4 is methyl.

Preference in the context of the present invention is also given to compounds of the invention in which n is the number zero.

Preference in the context of the present invention is also given to compounds of the invention in which n is the number 1, A is phenyl and R^5 is fluoro, chloro, trifluoromethyl, alkoxy, C_1-C_4 alkyl, phenyl or pyridyl, R^5 being positioned meta or para to the linkage site of the phenyl ring. By the linkage site of the phenyl ring is meant the carbon atom of the phenyl ring carrying R^5 to which the phenyl ring carrying R^5, in accordance with formula (I) or (Ia) as A, is attached to the remainder of the compound.

Preference in the context of the present invention is also given to compounds of the invention in which R^6 is C_3-C_6 alkyl or 3- to 6-membered cycloalkyl, especially isopropyl, isobutyl, 1-methylpropyl or cyclopentyl, very particularly isopropyl or cyclopentyl.

Preference in the context of the present invention is also given to compounds of the invention in which m is the number zero.

Preference in the context of the present invention is also given to compounds of the invention in which A is phenyl, naphthyl, pyridyl, thienyl, quinolinyl or isoquinolinyl.

Preference in the context of the present invention is also given to compounds of the invention in which A is phenyl.

Preference in the context of the present invention is also given to the following compounds:

6-fluoro-N-{(1*S*)-3-[((1*S*)-2-methyl-1-{[(3*R*,4*S*)-4-methyl-2,5-dioxo-3-pyrrolidinyl]-carbonyl}propyl)amino]-3-oxo-1-phenylpropyl}-2-pyridinecarboxamide

N-{(1*S*)-3-[((1*S*)-2-methyl-1-{[(3*R*,4*S*)-4-methyl-2,5-dioxo-3-pyrrolidinyl]carbonyl}-propyl)amino]-3-oxo-1-phenylpropyl}-3-quinolinecarboxamide

N-{(1*S*)-3-[((1*S*)-2-methyl-1-{[(3*R*,4*S*)-4-methyl-2,5-dioxo-3-pyrrolidinyl]-carbonyl}propyl)amino]-3-oxo-1-phenylpropyl}-4-phenyl-2-pyridinecarboxamide

N-[(1*S*)-3-({(1*S*)-1-cyclohexyl-2-[(3*R*,4*S*)-4-methyl-2,5-dioxo-3-pyrrolidinyl]-2-oxoethyl}amino)-3-oxo-1-phenylpropyl]-6-fluoro-2-pyridinecarboxamide

N-[(1*S*)-3-({1-cyclopentyl-2-[(3*R*,4*S*)-4-methyl-2,5-dioxo-3-pyrrolidinyl]-2-oxoethyl}amino)-3-oxo-1-phenylpropyl]-2-pyridinecarboxamide

(3*S*)-N-((1*S*)-2-methyl-1-{[(3*R*,4*S*)-4-methyl-2,5-dioxo-3-pyrrolidinyl]-carbonyl}propyl)-3-phenyl-3-[(2-thienylacetyl)amino]propanamide

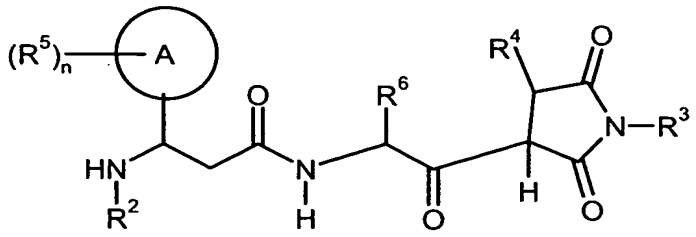
N-[(1*S*)-3-({(1*S*)-1-cyclopentyl-2-[(3*R*,4*S*)-4-methyl-2,5-dioxo-3-pyrrolidinyl]-2-oxoethyl}amino)-3-oxo-1-phenylpropyl]-4-phenyl-2-pyridinecarboxamide

N-[(1*S*)-3-({(1*S*)-1-cyclopentyl-2-[(3*R*,4*S*)-4-methyl-2,5-dioxo-3-pyrrolidinyl]-2-oxoethyl}amino)-3-oxo-1-phenylpropyl]-3-quinolinecarboxamide

N-[(1*S*)-3-({(1*S*)-1-cyclopentyl-2-[(3*R*,4*S*)-4-methyl-2,5-dioxo-3-pyrrolidinyl]-2-oxoethyl}amino)-3-oxo-1-phenylpropyl]-5-fluoro-1H-indole-2-carboxamide

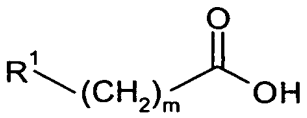
The invention further provides a process for preparing compounds of the formula (I), where

[A] compounds of the formula



(II),

in which R^2 to R^6, A and n are as defined above, are reacted with compounds of the formula



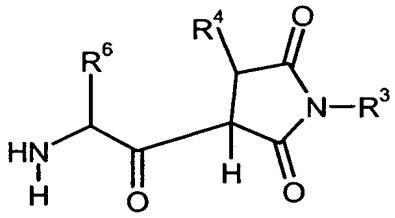
(III),

in which R^1 and m are as defined above,

it being possible for these to be in activated form if desired,

or

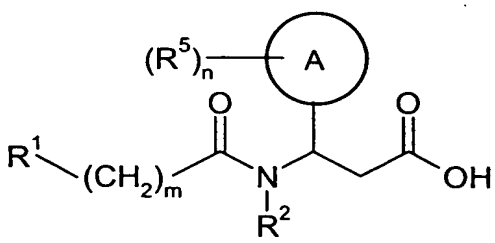
[B] compounds of the formula



(IV),

in which R^3, R^4 and R^6 are as defined above,

are reacted with compounds of the formula



(V),

in which R^1, R^2, R^5, A, m and n are as defined above,

it being possible for these to be in activated form if desired.

Suitable for converting the compounds into the activated form in the abovementioned processes are, for example, carbodiimides such as N,N'-diethyl-, N,N,'-dipropyl-, N,N'-diisopropyl-, N,N'-dicyclohexylcarbodiimide, N-(3-dimethylaminoisopropyl)-N'-ethylcarbodiimide hydrochloride (EDC) (optionally in the presence of pentafluorophenol (PFP)), N-cyclohexylcarbodiimide-N'-propyloxymethyl-polystyrene (PS-carbodiimide) or carbonyl compounds such as carbonyldiimidazole, or 1,2-oxazolium compounds such as 2-ethyl-5-phenyl-1,2-oxazolium-3-sulfate or 2-tert-butyl-5-methyl-isoxazolium perchlorate, or acylamino compounds such as 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, or propanephosphonic anhydride, or isobutyl chloroformate, or bis(2-oxo-3-oxazolidinyl)phosphoryl chloride or benzotriazolyloxytri(dimethylamino)phosphonium hexafluorophosphate, or O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU), 2-(2-oxo-1-(2H)-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU) or O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyl-uronium hexafluorophosphate (HATU), or 1-hydroxybenzotriazole (HOBt), or benzotriazol-1-yloxytris(dimethyl-amino)phosphonium hexafluorophosphate (BOP), or mixtures of these with bases.

Bases are, for example, alkali metal carbonates, such as sodium or potassium carbonate, or hydrogencarbonate, or organic bases such as trialkylamines, e.g. triethylamine, N-methylmorpholine, N-methylpiperidine, 4-dimethylaminopyridine or diisopropylethylamine.

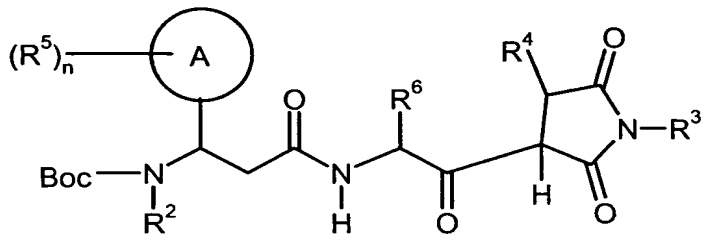
Preference is given to using HATU with diisopropylethylamine and using EDC with HOBt and triethylamine.

Suitable solvents in this context include inert organic solvents which do not change under the reaction conditions. These include halogenated hydrocarbons such as dichloromethane or trichloromethane, hydrocarbon such as benzene, xylene, toluene, hexane, cyclohexane, or petroleum fractions, nitromethane, dimethylformamide or acetonitrile or ethers such as diethyl ether, tetrahydrofuran or dioxane. It is also

possible to use mixtures of the solvents. Particular preference is given to dichloromethane or a mixture of dichloromethane and dimethylformamide.

Process [A]

The compounds of the formula (II) are known or can be prepared by admixing compounds of the formula



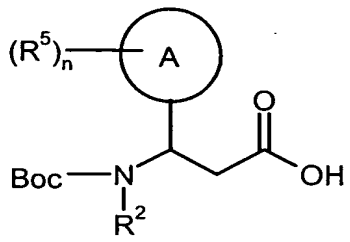
(VI),

in which R^2 to R^6, A and n are as defined above,

with acid, in particular with hydrochloric acid or trifluoroacetic acid. The compounds of the formula (II) are in this case obtained in the form of the corresponding salts, e.g., in the form of their hydrochlorides, and can be used further in this form or converted by chromatographic purification into their salt-free form.

Suitable solvents in this context include inert organic solvents which do not change under the reaction conditions. These include halogenated hydrocarbons such as dichloromethane or trichloromethane, hydrocarbons such as benzene, xylene, toluene, hexane, cyclohexane, or petroleum fractions, nitromethane, dimethylformamide or acetonitrile or ethers such as diethyl ether, tetrahydrofuran or dioxane. It is also possible to use mixtures of the solvents. Particular preference is given to the use of hydrochloric acid in dioxane or trifluoroacetic acid in dichloromethane.

The compounds of the formula (VI) are known or can be prepared by reacting compounds of the formula



(VII),

in which R^2, R^5, A and n are as defined above,

it being possible for these to be in activated form if desired.

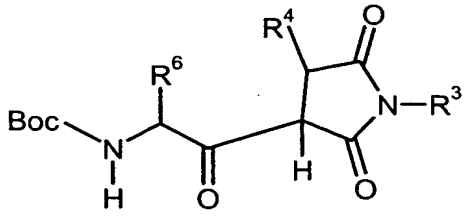
Suitable for converting the compounds into the activated form are, for example, carbodiimides such as N,N'-diethyl-, N,N,'-dipropyl-, N,N'-diisopropyl-, N,N'-dicyclohexylcarbodiimide, N-(3-dimethylaminoisopropyl)-N'-ethylcarbodiimide hydrochloride (EDC) (optionally in the presence of pentafluorophenol (PFP)), N-cyclohexylcarbodiimide-N'-propyloxymethyl-polystyrene (PS-carbodiimide) or carbonyl compounds such as carbonyldiimidazole, or 1,2-oxazolium compounds such as 2-ethyl-5-phenyl-1,2-oxazolium-3-sulfate or 2-tert-butyl-5-methyl-isoxazolium perchlorate, or acylamino compounds such as 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, or propanephosphonic anhydride, or isobutyl chloroformate, or bis(2-oxo-3-oxazolidinyl)phosphoryl chloride or benzotriazolyloxytri(dimethylamino)phosphonium hexafluorophosphate, or O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU), 2-(2-oxo-1-(2H)-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU) or O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyl-uronium hexafluorophosphate (HATU), or 1-hydroxybenzotriazole (HOBt), or benzotriazol-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate (BOP), or mixtures of these with bases.

Bases are, for example, alkali metal carbonates, such as sodium or potassium carbonate, or hydrogencarbonate, or organic bases such as trialkylamines, e.g. triethylamine, N-methylmorpholine, N-methylpiperidine, 4-dimethylaminopyridine or diisopropylethylamine.

Preference is given to using HATU and diisopropylethylamine or EDC with HOBt and triethylamine.

Suitable solvents in this context include inert organic solvents which do not change under the reaction conditions. These include halogenated hydrocarbons such as dichloromethane or trichloromethane, hydrocarbon such as benzene, xylene, toluene, hexane, cyclohexane, or petroleum fractions, nitromethane, dimethylformamide or acetonitrile or ethers such as diethyl ether, tetrahydrofuran or dioxane. It is also possible to use mixtures of the solvents. Particular preference is given to a mixture of dichloromethane and dimethylformamide.

The compounds of the formula (IV) are known from the literature or new and can be prepared by admixing compounds of the formula



(VIII),

in which R^3, R^4 and R^6 are as defined above,

with acid, in particular with hydrochloric acid or trifluoroacetic acid.

Suitable solvents in this context include inert organic solvents which do not change under the reaction conditions. These include halogenated hydrocarbons such as

dichloromethane or trichloromethane, hydrocarbons such as benzene, xylene, toluene, hexane, cyclohexane, or petroleum fractions, nitromethane, dimethylformamide or acetonitrile or ethers such as diethyl ether, tetrahydrofuran or dioxane. It is also possible to use mixtures of the solvents. Particular preference is given to the use of hydrochloric acid in dioxane or trifluoroacetic acid in dichloromethane.

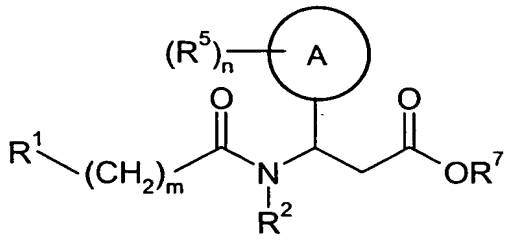
The compounds of the formula (VII) are known or can be prepared by procedures known from the literature. (With regard to the preparation of aromatic beta-amino acids see for example: S. Rault, P. Dallemagne, M. Robba, *Bull. Soc. Chim. Fr.*, 1987, 1079-1083; S.G. Davies et al., *J. Chem. Soc., Chem. Commun.* 1993, 1153-1155; V. A. Soloshonok et al., *Tetrahedron Asymmetry*, 1995, 1601-1610; regarding the reaction to form the tert-butoxycarbonyl-protected compounds see T.W. Greene, P.G.M. Wuts, Protective Groups in Organic Synthesis, 3rd Edt. 1999, J. Wiley & Sons, Inc.).

The compounds of the formula (VIII) are known or can be prepared by methods known from the literature. (Cf., e.g., S. G. Davies, D. J. Dixon, *J. Chem. Soc., Perkin Trans. 1*, 1998, *17*, 2635-2643; A. V. Rama Rao, A. K. Singh, Ch. V. N. S. Varaprasad, *Tetrahedron Letters*, 1991, *32*, 4393-4396).

The compounds of the formula (III) are known or can be prepared by methods known from the literature (Houben-Weyl, Methoden der organischen Chemie, vol. E5, Carboxylic acids and carboxylic acid derivatives, Thieme Verlag, Stuttgart, 1985).

Process [B]

The compounds of the formula (V) are known from the literature or new and can be prepared by hydrolyzing compounds of the formula

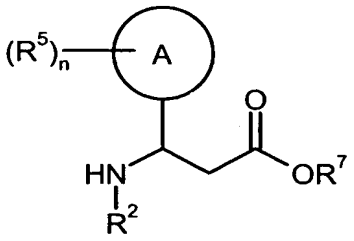


(IX),

in which R^1, R^2, R^5, A, m and n are as defined above and
R^7 is an alkyl radical.

The hydrolysis can be carried out in accordance with standard methods, e.g., in a mixture of ethanol and water with 40% strength sodium hydroxide solution at room temperature or in a mixture of dioxane and water with 10% strength methanolic potassium hydroxide solution.

The compounds of the formula (IX) are known from the literature or new and can be prepared by reacting compounds of the formula



(X),

in which R^2, R^5, R^7, A and n are as defined above,

with compounds of the formula (III), it being possible for these to be in activated form if desired.

Suitable for converting the compounds into the activated form in the abovementioned processes are, for example, carbodiimides such as N,N'-diethyl-, N,N,'-dipropyl-, N,N'-diisopropyl-, N,N'-dicyclohexylcarbodiimide, N-(3-dimethylaminoisopropyl)-

N'-ethylcarbodiimide hydrochloride (EDC) (optionally in the presence of pentafluorophenol (PFP)), N-cyclohexylcarbodiimide-N'-propyloxymethyl-polystyrene (PS-carbodiimide) or carbonyl compounds such as carbonyldiimidazole, or 1,2-oxazolium compounds such as 2-ethyl-5-phenyl-1,2-oxazolium-3-sulfate or 2-tert-butyl-5-methyl-isoxazolium perchlorate, or acylamino compounds such as 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, or propanephosphonic anhydride, or isobutyl chloroformate, or bis(2-oxo-3-oxazolidinyl)phosphoryl chloride or benzotriazolyloxytri(dimethylamino)phosphonium hexafluorophosphate, or O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU), 2-(2-oxo-1-(2H)-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU) or O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyl-uronium hexafluorophosphate (HATU), or 1-hydroxybenzotriazole (HOBt), or benzotriazol-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate (BOP), or mixtures of these with bases.

Bases are, for example, alkali metal carbonates, such as sodium or potassium carbonate, or hydrogencarbonate, or organic bases such as trialkylamines, e.g., triethylamine, N-methylmorpholine, N-methylpiperidine, 4-dimethylaminopyridine or diisopropylethylamine.

Preference is given to using HATU with diisopropylethylamine and using EDC with HOBt and triethylamine.

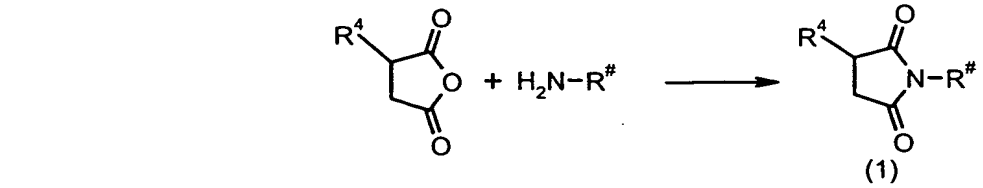
Suitable solvents in this context include inert organic solvents which do not change under the reaction conditions. These include halogenated hydrocarbons such as dichloromethane or trichloromethane, hydrocarbon such as benzene, xylene, toluene, hexane, cyclohexane, or petroleum fractions, nitromethane, dimethylformamide or acetonitrile or ethers such as diethyl ether, tetrahydrofuran or dioxane. It is also possible to use mixtures of the solvents. Particular preference is given to dichloromethane or a mixture of dichloromethane and dimethylformamide.

The compounds of the formula (X) are known from the literature or new and can be prepared in analogy to methods known from the literature (With regard to the preparation of aromatic beta-amino acids and their conversion into the corresponding alkyl esters see for example: S. Rault, P. Dallemagne, M. Robba, *Bull. Soc. Chim. Fr.*, 1987, 1079-1083; S.G. Davies et al., *J. Chem. Soc., Chem. Commun.* 1993, 1153-1155; V. A. Soloshonok et al., *Tetrahedron Asymmetry*, 1995, 1601-1610; S. J. Faulconbridge et al., *Tetrahedron Letters*, 2000, *41*, 2679-2682).

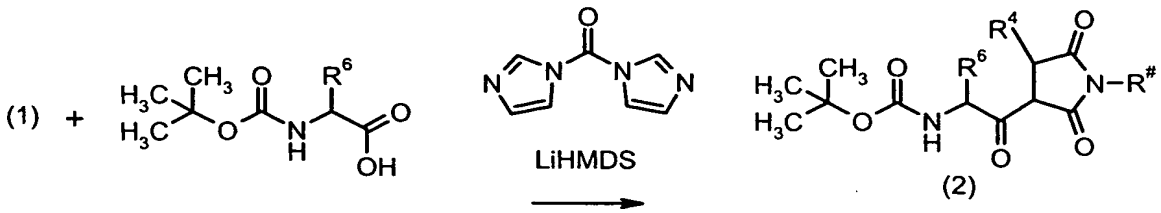
Synthesis may also take place on a polymeric support. In that case R^2 in the synthesis sequence is a polymer (resin), preference being given to the use of 4-(4-formyl-3-methoxyphenoxy)butyryl-aminomethyl-polystyrene or another resin in which a polymeric backbone such as polystyrene or block copolymers of polystyrene with ethylene glycol has attached to it via a linker group such as 3-methoxyphenoxyethyl, 3,5-dimethoxyphenoxyethoxymethyl or 3-methoxyphenoxybutyrylaminomethyl a formyl radical or another radical which allows amines to be attached to the polymeric support.

The preparation of the compounds of the invention can be illustrated by the following synthesis schemes:

Starting compounds:

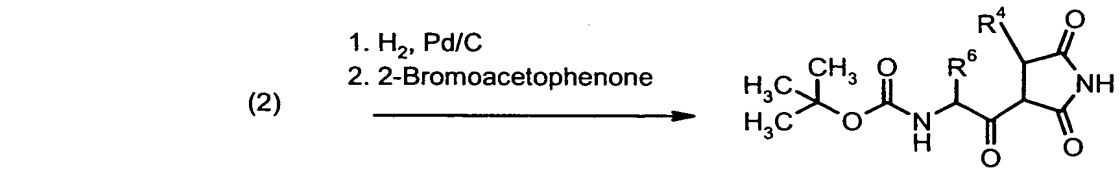


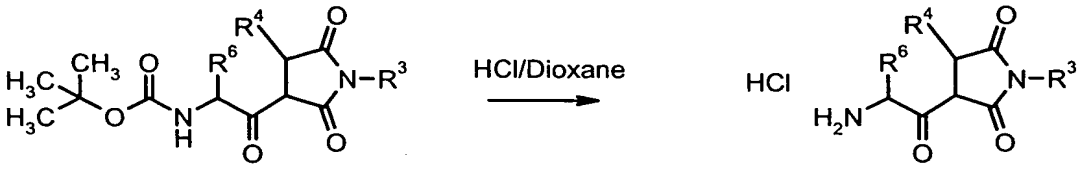
(1)

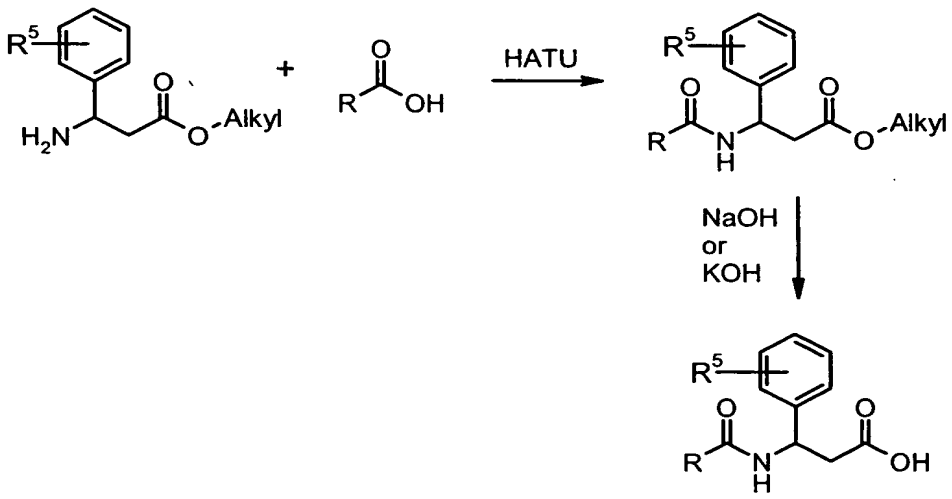


(2)

if R# = OBn:

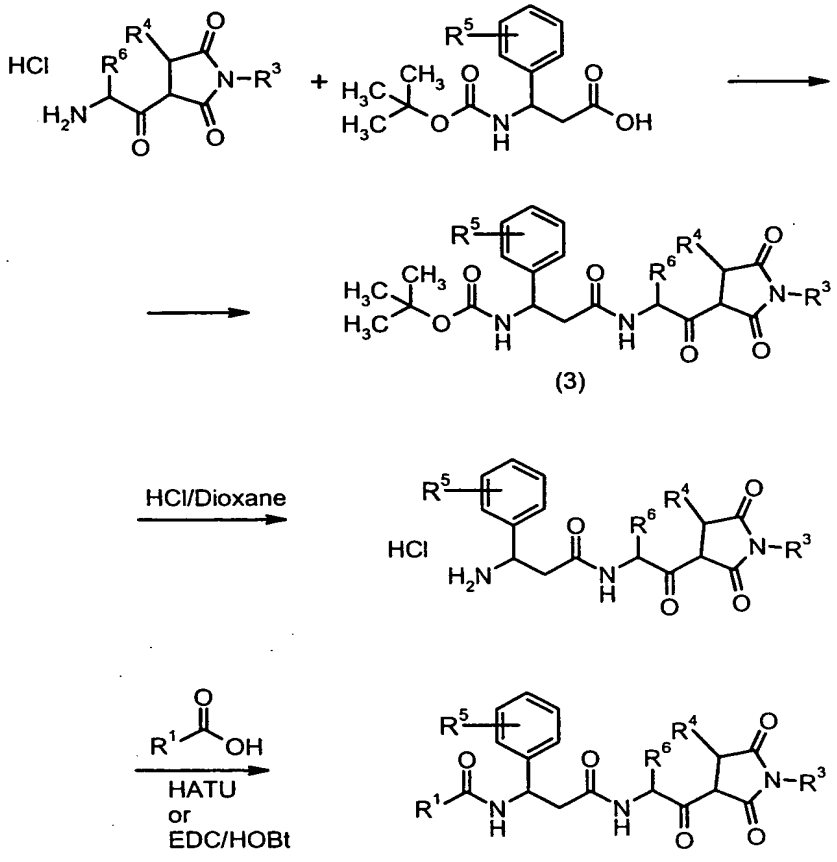






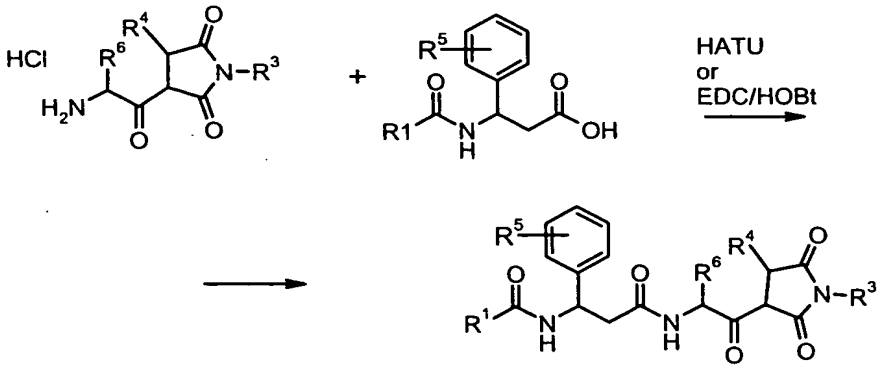
Preparation examples:

Method A

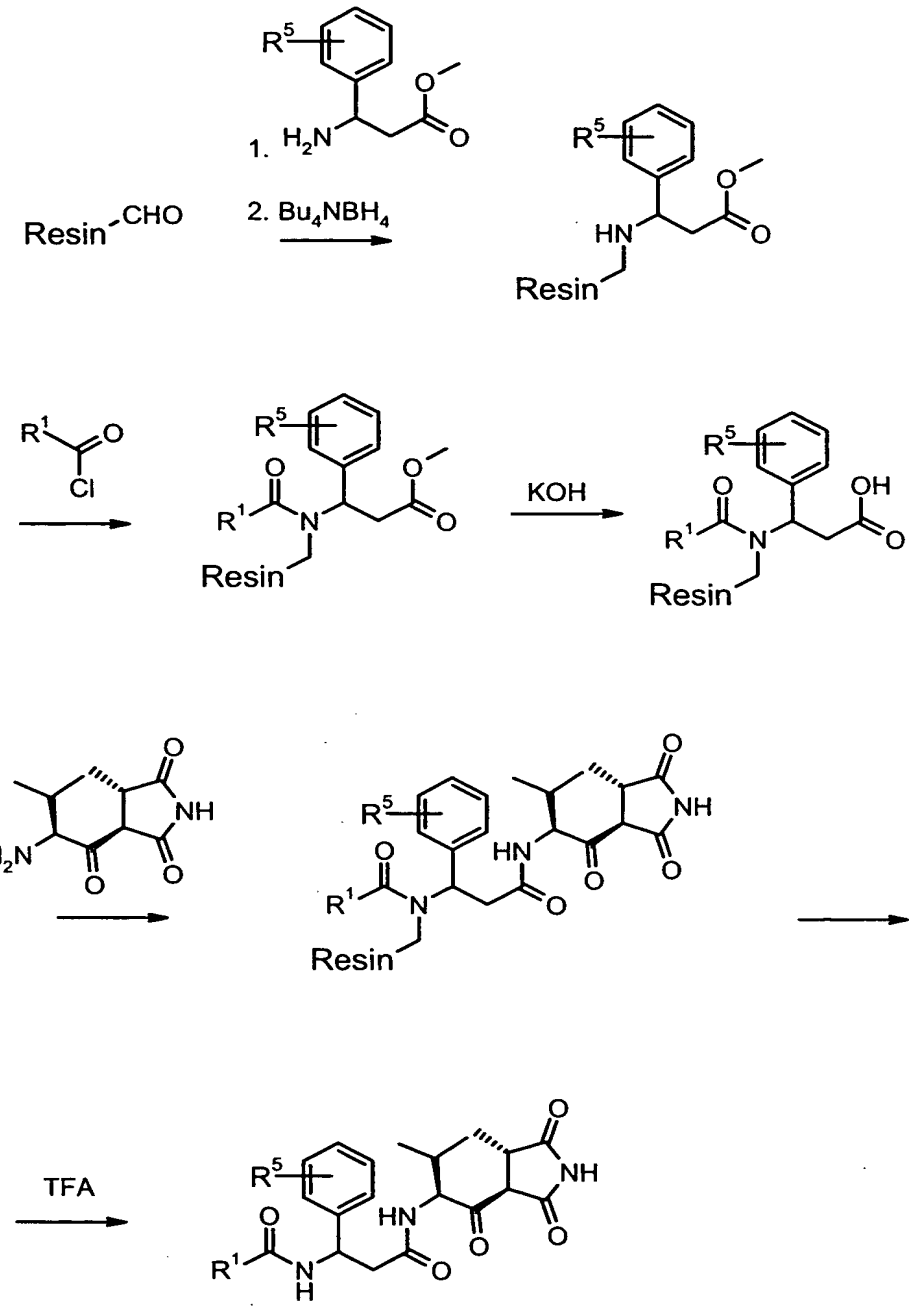


(3)

Method B



Solid phase synthesis:



The present invention further provides compounds of the formula (I) for controlling diseases, particularly bacterial diseases, and also medicinal products comprising compounds of the formula (I) and auxiliaries, and also for the use of compounds of the formula (I) for producing a medicinal product for treating bacterial diseases.

The formulations of the invention are particularly active against bacteria and bacterialike microorganisms. They are therefore particularly suitable for the prophylaxis and chemotherapy of local and systemic infections in human and veterinary medicine that are induced by these pathogens.

By way of example it is possible to treat and/or prevent local and/or systemic diseases caused by the following pathogens or by combinations of the following pathogens:

Gram-positive cocci, e.g., staphylococci (Staph. aureus, Staph. epidermidis), enterococci (E. faecalis, E. faecius) and streptococci (Strept. agalactiae, Strept. pneumoniae); gram-negative cocci (Neisseria gonorrhoeae) and gram-negative rods such as enterobacteria, e.g., Escherichia coli, Haemophilus influenzae, citrobacter (Citrob. freundii, Citrob. divernis), salmonella and shigella; and also klebsiellas (Klebs. pneumoniae, Klebs. oxytocy), enterobacter (Ent. aerogenes, Ent. agglomerans), hafnia, serratia (Serr. marcescens), providencia, yersinia, and also the genus Acinetobacter. The antibacterial spectrum further embraces strictly anaerobic bacteria such as Bacteroides fragilis, representatives of the genus Peptococcus, Peptostreptococcus and the genus Clostridium; and also mycoplasmas (M. pneumoniae, M. hominis, M. urealyticum) and mycobacteria, e.g., Mycobacterium tuberculosis.

The above listing of pathogens should be interpreted merely as exemplary and in no way as restrictive. Examples that may be mentioned of diseases which may be caused by the stated pathogens or combination infections and which may be prevented, remedied or cured by the formulations of the invention include the following:

Infectious diseases in humans, such as septic infections, bone and joint infections, skin infections, postoperative wound infections, abscesses, phlegmons, wound infections, infected burns, burn wounds, infections in the oral region, infections following dental operations, septic arthritis, mastitis, tonsillitis, genital infections and eye infections.

As well as in humans, bacterial infections in other species too can be treated. Examples that may be mentioned include the following:

pigs: coli diarrhea, enterotoxemia, sepsis, dysenteria, salmonellosis, metritis-mastitis-agalactia syndrome, mastitis;

ruminants (cattle, sheep, goats): diarrhea, sepsis, bronchopneumonia, salmonellosis, pasteurellosis, mycoplasmosis, genital infections;

horses: bronchopneumonias, joint ill, puerperal and postpartum infections, salmonellosis;

dogs and cats: bronchopneumonia, diarrhea, dermatitis, otitis, urinary tract infections, prostatitis;

poultry (chickens, turkeys, quails, pigeons, ornamental birds and others): mycoplasmosis, E. coli infections, chronic respiratory tract diseases, salmonellosis, pasteurellosis, psittacosis.

It is also possible to treat bacterial diseases associated with the breeding and keeping of farmed and ornamental fish, in which case the antibacterial spectrum extends beyond the aforementioned pathogens to embrace further pathogens such as Pasteurella, Brucella, Campylobacter, Listeria, Erysipelothris, Corynebacteria, Borellia, Treponema, Nocardia, Rickettsi, Yersinia, for example.

The active ingredient may act systemically and/or locally. For that purpose it can be administered in appropriate manner, such as orally, parenterally, pulmonically, nasally, sublingually, lingually, buccally, rectally, transdermally, conjunctivally, otically or as an implant.

For these administration routes the active ingredient can be administered in suitable administration forms.

Administration forms suitable for oral administration are known such forms which deliver the active ingredient rapidly and/or in a modified way, such as tablets (uncoated and coated tablets, such as film-coated tablets or tablets provided with enteric coatings), capsules, sugar-coated tablets, granules, pellets, powders, emulsions, suspensions and solutions.

Parenteral administration can be made with avoidance of an absorption step (intravenously, intraarterially, intracardially, intraspinally or intralumbarly) or with inclusion of absorption (intramuscularly, subcutaneously, intracutaneously, percutaneously, or intraperitoneally). Administration forms suitable for parenteral administration include preparations for injection and infusion in the form of solutions, suspensions, emulsions, lyophilisates and sterile powders.

Preference is given to parenteral administration, more particularly intravenous administration.

Examples suitable for the other administration routes are pharmaceutical forms for inhalation (including powder inhalers, nebulizers), nasal drops/solutions, sprays; capsules or tablets to be administered lingually, sublingually or buccally, suppositories, ear and eye preparations, vaginal capsules, aqueous suspensions (lotions, shaking mixtures), lipophilic suspensions, ointments, creams, milk, pastes, dusting powders or implants.

The active ingredients can be converted in conventional manner into the stated administration forms. This is done with the use of inert, nontoxic, pharmaceutically appropriate auxiliaries (excipients). These include, among others, carriers (e.g., microcrystalline cellulose), solvents (e.g. liquid polyethylene glycols), emulsifiers

(e.g., sodium dodecyl sulfate), dispersants (e.g., polyvinylpyrrolidone), synthetic and natural biopolymers (e.g., albumen), stabilizers (e.g., antioxidants such as ascorbic acid), colorants (e.g., inorganic pigments such as iron oxides) or flavor and/or odor masking agents.

It has generally proven advantageous in the case of parenteral administration to administer amounts of about 5 to 250 mg/kg body weight per 24 hours in order to achieve effective results. In the case of oral administration the amount is about 5 to 100 mg/kg body weight per 24 hours.

It may nevertheless be necessary, where appropriate, to deviate from the amounts specified, specifically as a function of body weight, administration route, individual response to the active ingredient, type of formulation, and time or interval at which administration takes place.

The percentages in the tests and examples below, unless stated otherwise, are percentages by weight; parts are parts by weight. Solvent ratios, dilution ratios and concentration figures for liquid/liquid solutions are based in each case on the volume.

A. Examples

Reaction schemes which are shown for general procedures show a selection of examples, but can be employed in each case for all of the examples which refer to them.

A. Abbreviations:

Boc	tert-butoxycarbonyl
$CDCl_3$	deuterochloroform
DCI	direct chemical ionization
DIEA	*N,N*-diisopropylethylamine
DMSO	dimethyl sulfoxide
EDC	N-(3-dimethylaminoisopropyl)-N′-ethylcarbodiimide hydrochloride
eq.	equivalent
ES	electrospray ionization (for MS)
Fmoc	fluorenylmethoxycarbonyl
HATU	*O*-(7-azabenzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate
h	hour
HOBt	1-hydroxylbenzotriazole
HPLC	high-pressure, high-performance liquid chromatography
LC-MS	liquid chromatography-coupled mass spectroscopy
MS	mass spectroscopy
MW	molecular weight [g/mol]
NMR	nuclear magnetic resonance spectroscopy
PS-DIEA	*N,N*-diisopropylethylamine-polystyrene (Resin)
R_f	retention index (for TLC)
RP-HPLC	reverse phase HPLC
RT	room temperature

R_t	retention time (for HPLC)
THF	tetrahydrofuran

HPLC and LC-MS methods:

Method 1: column: Kromasil C18, L-R temperature: 30°C, flow rate = 0.75 ml min^{-1}, mobile phase: A = 0.01 M $HClO_4$, B = acetonitrile, gradient: → 0.5 min 98%A → 4.5 min 10%A → 6.5 min 10%A.

Method 2: column: Kromasil C18 60*2 mm, L-R temperature: 30°C, flow rate = 0.75 ml min^{-1}, mobile phase: A = 0.01 M H_3PO_4, B = acetonitrile, gradient: → 0.5 min 90%A → 4.5 min 10%A → 6.5 min 10%A.

Method 3: column: Kromasil C18 60*2 mm, L-R temperature: 30°C, flow rate = 0.75 ml min^{-1}, mobile phase: A = 0.005 M $HClO_4$, B = acetonitrile, gradient: → 0.5 min 98%A → 4.5 min 10%A → 6.5 min 10%A.

Method 4: column: Symmetry C18 2.1x150 mm, column oven: 50°C, flow rate = 0.6 ml min^{-1}, mobile phase: A = 0.6 g 30% strength hydrochloric acid/ 1 water, B = acetonitrile, gradient: 0.0 min 90%A → 4.0 min 10%A → 9 min 10%A.

Method 5: Instrument: Micromass Quattro LCZ
Column: Symmetry C18, 50 mm x 2.1 mm, 3.5 µm, temperature: 40°C, flow rate = 0.5 ml min^{-1}, mobile phase A = acetonitrile + 0.1% formic acid, mobile phase B = water + 0.1% formic acid, gradient: 0.0 min 10% A → 4 min 90% A → 6 min 90% A.

Method 6: Instrument: Micromass Platform LCZ
Column: Symmetry C18, 50 mm x 2.1 mm, 3.5 µm, temperature: 40°C, flow rate = 0.5 ml min^{-1}, mobile phase A = acetonitrile + 0.1% formic acid, mobile phase B =

water + 0.1% formic acid, gradient: 0.0 min 10% A → 4 min 90% A → 6 min 90% A.

Method 7: Instrument: Micromass Quattro LCZ
Column: Symmetry C18, 50 mm x 2.1 mm, 3.5 µm, temperature: 40°C, flow rate = 0.5 ml min^{-1}, mobile phase A = acetonitrile + 0.1% formic acid, mobile phase B = water + 0.1% formic acid, gradient: 0.0 min 5% A → 1 min 5% A → 5 min 90% A → 6 min 90% A.

Method 8: column: Symmetry C18 2.1 x 150 mm, 5 µm, column oven: 70°C, flow rate = 0.9 ml min^{-1}, mobile phase: A = acetonitrile, B = 0.3 g 30% strength hydrochloric acid/ l water, gradient: 0.0 min 2% A → 2.5 min 95% A → 5 min 95% A.

Method 9: column: Symmetry C18 3.9 x 150 mm, column oven: 40°C, flow rate = 1.5 ml min^{-1}, mobile phase: A = water + 0.05% H_3PO_4, , B = acetonitrile, gradient: 0.0 min 10% B → 0.6 min 10% B → 3.8 min 100% B → 5.0 min 100% B.

Method 10: Instrument: Waters Alliance 2790 LC; column: Symmetry C18, 50 mm x 2.1 mm, 3.5 µm; mobile phase A: water + 0.1% formic acid, mobile phase B: acetonitrile + 0.1% formic acid; gradient: 0.0 min 5% B → 5.0 min 10% B → 6.0 min 10% B; temperature: 50°C, flow rate: 1.0 ml/min, UV detection: 210 nm.

Method 11: Instrument type MS: Micromass ZQ; instrument type HPLC: Waters Alliance 2790; column: Symmetry C 18, 50 mm x 2.1 mm, 3.5 µm; mobile phase B: acetonitrile + 0.05% formic acid, mobile phase A: water + 0.05% formic acid; gradient: 0.0 min 10%B → 3.5 min 90% B → 5.5 min 90% B; oven: 50 °C, flow rate: 0.8 ml/min, UV detection: 210 nm.

Method 12: Instrument: Waters Alliance 2790 LC; column: Symmetry C18, 50 mm x 2.1 mm, 3.5 µm; mobile phase A: water + 0.05% formic acid, mobile phase B:

acetonitrile + 0.05% formic acid; gradient: 0.0 min 5% B → 4.5 min 10% B → 5.5 min 10% B; temperature: 50°C, flow rate: 1.0 ml/min, UV detection: 210 nm.

Method 13: Instrument: Micromass Quattro LCZ, HP1100; column: Symmetry C18, 50 mm x 2.1 mm, 3.5 µm; mobile phase A: water + 0.05% formic acid, mobile phase B: acetonitrile + 0.05% formic acid; gradient: 0.0 min 90% A → 4.0 min 10% A → 6.0 min 10% A; Oven: 40°C, flow rate: 0.5 ml/min, UV detection: 208-400 nm.

Method 14: Instrument: Micromass Platform LCZ, HP1100; column: Symmetry C18, 50 mm x 2.1 mm, 3.5 µm; mobile phase A: water + 0.05% formic acid, mobile phase B: acetonitrile + 0.05% formic acid; gradient: 0.0 min 90% A → 4.0 min 10% A → 6.0 min 10% A; oven: 40°C, flow rate: 0.5 ml/min, UV detection: 208-400 nm.

Method 15: Instrument: Waters Alliance 2790 LC; column: Symmetry C18, 50 mm x 2.1 mm, 3.5 µm; mobile phase A: water + 0.05% formic acid, mobile phase B: acetonitrile + 0.05% formic acid; gradient: 0.0 min 10% B → 4.0 min 90% B → 6.0 min 90% B; temperature: 50°C, flow rate: 0.0 min 0.5 ml/min → 4.0 min 0.8 ml/min, UV detection: 210 nm.

Method 16: Instrument type MS: Micromass ZQ; intrument type HPLC: Waters Alliance 2790; column: Symmetry C 18, 50 mm x 2.1 mm, 3.5 µm; mobile phase B: acetonitrile + 0.05% formic acid, mobile phase A: water + 0.05% formic acid; gradient: 0.0 min 5% B 4.5 min 90% B 5.5 min 90% B; oven: 50°C, flow rate: 1.0ml/, UV detection: 210 nm.

Method 17: Instrument type MS: Micromass ZQ; instrument type HPLC: Waters Alliance 2790; column: Uptisphere C 18, 50 mm x 2.0 mm, 3.0 µm; mobile phase B: acetonitrile + 0.05% formic acid, mobile phase A: water + 0.05% formic acid; gradient: 0.0 min 5% B → 2.0 min 40% B → 4.5 min 90% B→ 5.5 min 90% B; oven: 45°C, flow rate: 0.0 min 0.75 ml/min → 4.5 min 0.75 ml/min→ 5.5 min 1.25 ml/min, UV detection: 210 nm.

Method 18: Instrument: Micromass Platform LCZ with HPLC Agilent series 1100; column: Grom-SIL120 ODS-4 HE, 50 mm x 2.0 mm, 3 µm; mobile phase A: 1 l water + 1 ml 50% strength formic acid, mobile phase B: 1 l acetonitrile + 1 ml 50% strength formic acid ; gradient: 0.0 min 100% A → 0.2 min 100% A → 2.9 min 30% A → 3.1 min 10% A → 4.5 min 10% A; oven: 55°C, flow rate: 0.8 ml/min, UV detection: 208-400 nm.

Method 19: Instrument: Micromass Quattro LCZ, with HPLC Agilent series 1100; column: Grom-SIL120 ODS-4 HE, 50 mm x 2.0 mm, 3 µm; mobile phase A: 1 l water + 1 ml 50% strength formic acid, mobile phase B: 1 l acetonitrile + 1 ml 50% strength formic acid; gradient: 0.0 min 100% A → 0.2 min 100% A → 2.9 min 30% A → 3.1 min 10% A → 4.5 min 10% A; oven: 55°C, flow rate: 0.8 ml/min, UV detection: 208-400 nm.

Method 20: Instrument type MS: Micromass ZQ; instrument type HPLC: Waters Alliance 2790; column: Grom-Sil 120 ODS-4 HE 50 x 2 mm, 3.0 µm; mobile phase B: acetonitrile + 0.05% formic acid, mobile phase A: water + 0.05% formic acid; gradient: 0.0 min 5% B → 2.0 min 40% B → 4.5 min 90% B→ 5.5 min 90% B; oven: 45°C; flow rate: 0.0 min 0.75 ml/min → 4.5 min 0.75 ml/min→ 5.5 min 1.25 ml/min; UV detection: 210 nm.

Method 21: Instrument type MS: Micromass ZQ; instrument type HPLC: Waters Alliance 2790; column: Grom-Sil 120 ODS-4 HE 50x2 mm, 3.0 µm; mobile phase B: acetonitrile + 500 ul 50 % strength formic acid / l; mobile phase A: water + 500 µl 50 % strength formic acid / l; gradient: 0.0 min 0% B → 0.2 min 0% B → 2.9 min 70 %B→ 3.1 min 90% B → 4.5 min 90% B, oven: 50 °C, flow rate:0.8 ml/min; UV detection: 210 nm.

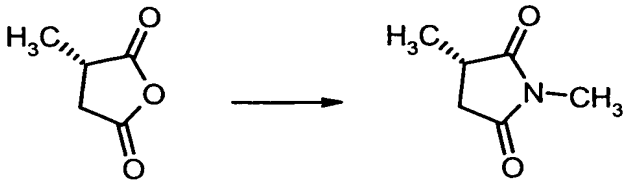
Method 22: Instrument: Micromass Quattro LCZ with HPLC Agilent series 1100; column: UPTISPHERE HDO, 50 mm x 2.0 mm, 3 µm; mobile phase A: 1 l water +

1ml 50 % strength formic acid, mobile phase B: 1 l acetonitrile + 1 ml 50% strength formic acid; gradient: 0.0 min 100% A → 0.2 min 100% A → 2.9 min 30% A → 3.1 min 10% A → 4.5 min 10% A; oven: 55°C, flow rate: 0.8 ml/min, UV detection: 208-400 nm.

Starting compounds:

Example 1A

(3*S*)-1,3-Dimethyl-2,5-pyrrolidinedione



600 mg (5.26 mmol) of (3*S*)-3-methyldihydro-2,5-furandione (preparation: S. G. Davies, D. J. Dixon, *J. Chem. Soc., Perkin Trans. 1*, **1998**, *17*, 2635 – 2643) are introduced to a vessel together with 559 mg (0.77 ml, 5.52 mmol) of triethylamine in 5 ml of dichloromethane at 0°C, and 373 mg (5.52 mmol) of methylamine hydrochloride are added. The reaction mixture is stirred at room temperature overnight and then 938 mg (5.78 mmol) of N,N-carbonyldiimidazole are added in portions. The mixture is stirred at room temperature for 1.5 h and at reflux temperature for 30 minutes. After it has cooled to room temperature the reaction mixture is washed with 5% strength hydrochloric acid and water, the organic phase is dried over magnesium sulfate, filtered and concentrated and the product is dried under a high vacuum. This gives 605 mg of the product (88% of theory).

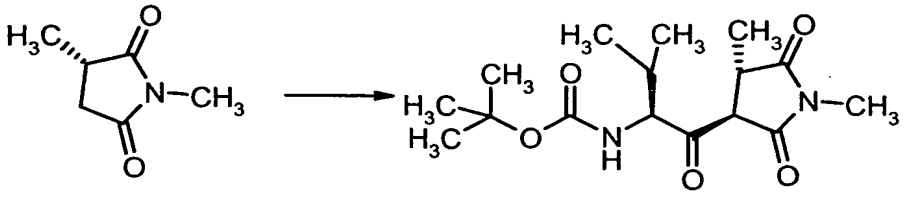
MS (ES+): m/z (%) = 128 ($M+H^+$) (100).

HPLC (method 6): R_t = 0.81 min.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.10 (dd, 1 H), 2.99 (s, 3 H), 2.90-2.82 (m, 1 H), 2.32 (dd, 1 H), 1.35 (d, 3 H).

Example 2A

(3*R*,4*S*)-3-[(2*S*)-2-(*tert*-Butoxycarbonyl)amino-3-methylbutanoyl]-1,4-dimethyl-2,5-pyrrolidinedione



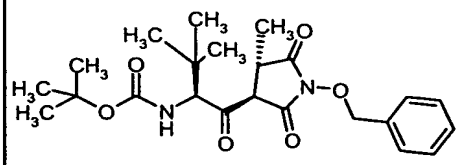
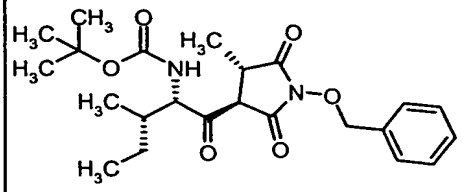
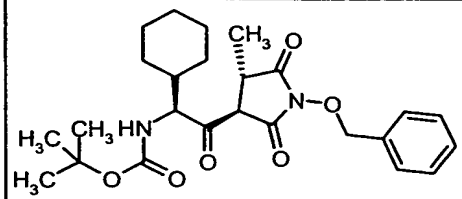
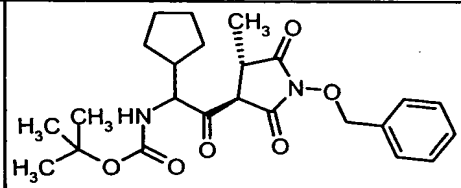
684 mg (3.15 mmol) of N-(*tert*-butoxycarbonyl)-L-valine and 561 mg (3.46 mmol) of N,N-carbonyldiimidazole are stirred in 4 ml of tetrahydrofuran at room temperature for 2 h. Then 400 mg (3.15 mmol) of (3*S*)-3-1,3-dimethyl-2,5-pyrrolidinedione are added to this mixture and the whole mixture is added dropwise over the course of 30 minutes to 6.3 ml of a 1 molar solution of lithium hexamethyldisilazide in THF, which has been cooled to –65°C. After the end of the addition stirring is continued at –65°C for 15 minutes more, and then 6 ml of saturated aqueous ammonium chloride are added. After the reaction mixture has been warmed to room temperature it is diluted with diethyl ether and the organic phase is washed with saturated aqueous sodium chloride solution and subsequently concentrated. The crude product is purified by RP-HPLC (mobile phase: water-acetonitrile, gradient). This gives 223 mg (22% of theory) of the desired product.

MS (ES-): m/z (%) = 325 ($M-H^+$) (35).

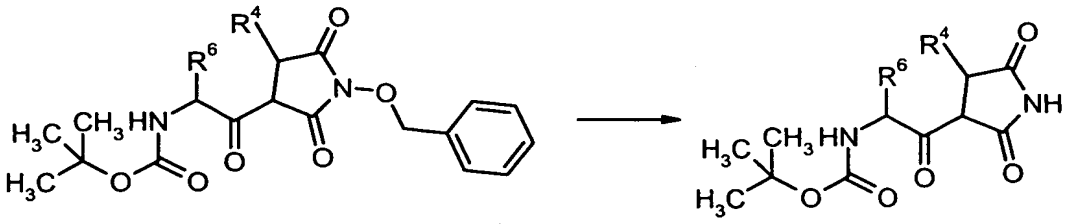
HPLC (method 5): R_t = 3.99 min.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.70 (br. d, 1 H), 4.57 (dd, 1 H), 3.78 (d, 1 H), 3.47-3.30 (m, 1 H), 2.98 (s, 3 H), 2.50- 2.32 (m, 1 H), 1.46 (s, 9 H), 1.32 (d, 3 H), 1.02 (d, 3 H), 0.80 (d, 3 H).

In the same way it is possible by reacting the corresponding N-*tert*-butoxycarbonyl-protected amino acids with (3*S*)-1-(benzyloxy)-3-methyl-2,5-pyrrolidinedione (preparation: S. G. Davies, D. J. Dixon, *J. Chem. Soc., Perkin Trans. 1*, **1998**, *17*, 2635 – 2643) to prepare the following derivatives:

Example	Structure	MW	MS	HPLC
3A		432.52	MS (ES-), m/z (%): 431 $(M-H)^-$ (100)	HPLC (method 6): R_t = 4.87 min
4A		432.51	MS (ES-), m/z (%): 431 $(M-H)^-$ (100)	HPLC (method 10): R_t = 4.10 min
5A		458.55	MS (ES-), m/z (%): 457 $(M-H)^-$ (100)	HPLC (method 12): R_t = 4.12 min
6A		444.53	MS (ES-), m/z (%): 443 $(M-H)^-$ (100)	HPLC (method 12): R_t = 3.97 min

General instructions A: Reductive deprotection of 1-benzyloxy-2,5-pyrrolidinediones

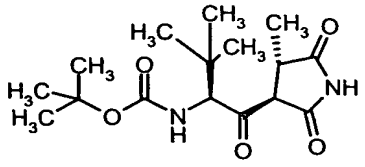
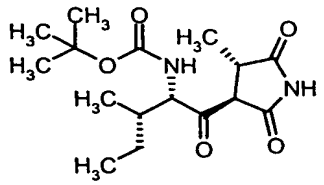
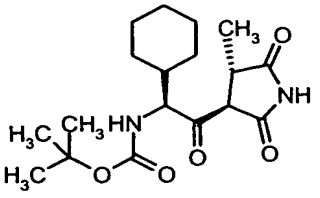


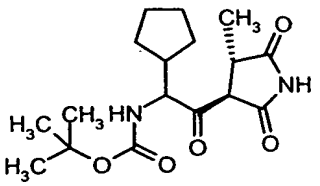
Deprotection takes place in a manner similar to that of S. G. Davies, D. J. Dixon, *J. Chem. Soc., Perkin Trans. 1,* 1998, *17*, 2635-2643.

The 1-benzyloxy-2,5-pyrrolidinedione (1 eq.) is dissolved in methanol (about 0.02 mol/l), a catalytic amount of palladium-on-carbon (10%) is added, and the

mixture is stirred under a hydrogen atmosphere (atmospheric pressure) for 1 h. The reaction mixture is then filtered and concentrated. The residue is dissolved in acetonitrile (about 0.05 mol/l) and added dropwise at room temperature to a solution of 2-bromoacetophenone (1 eq) in acetonitrile (about 0.03 mol/l) at room temperature. Thereafter over a period of 2 h, 1.5 eq. of triethylamine in acetonitrile (about 0.35 mol/l) are added dropwise to the reaction mixture. The reaction mixture is stirred at room temperature overnight and concentrated and the crude product is purified by means of RP-HPLC (mobile phase: acetonitrile/water + 0.3 ml 37% strength hydrochloric acid/l, gradient).

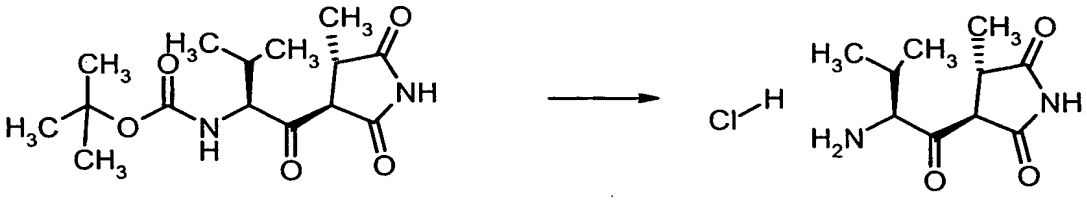
In accordance with general instructions A it is possible to obtain the following compounds:

Example	Structure	MW	MS	HPLC
7A		326.40	MS (ES+), m/z (%): 327 $(M+H)^+$ (100)	HPLC (method 5): R_t = 3.87 min
8A		326.40	MS (ES+), m/z (%): 349 $(M+Na)^+$ (100)	HPLC (method 12): R_t = 2.97 min
9A		352.43	MS (ES-), m/z (%): 351 $(M-H)^-$ (100)	HPLC (method 12): R_t = 3.23 min

Example	Structure	MW	MS	HPLC
10A		338.40	MS (ES-), m/z (%): 337 $(M-H)^-$ (100)	HPLC (method 13): R_t = 4.16 min

Example 11A

(3*R*,4*S*)-3-[(2*S*)-2-Amino-3-methylbutanoyl]-4-methyl-2,5-pyrrolidinedione hydrochloride



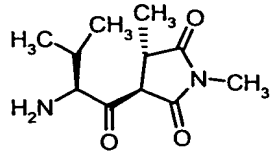
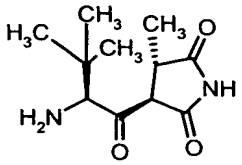
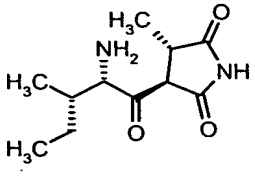
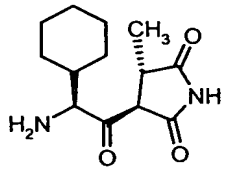
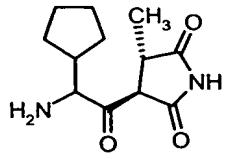
A solution, cooled at 0°C, of 4.40 g (14.09 mmol) of (3*R*,4*S*)-3-[(2*S*)-2-(*tert*-butoxycarbonyl)amino-3-methylbutanoyl]-4-methyl-2,5-pyrrolidinedione (preparation: S. G. Davies, D. J. Dixon, *J. Chem. Soc., Perkin Trans. 1*, **1998**, *17*, 2635 – 2643) in dioxane is admixed dropwise with 35 ml of 4N hydrochloric acid solution in 1,4-dioxane. When the addition is at an end the mixture is warmed to room temperature and stirred for 2 h, after which the mixture is concentrated under reduced pressure. The crude product can be used directly in the next stage. If desired the residue is treated with diethyl ether and the crystals precipitated are filtered off and dried under a high vacuum.

Yield: 2.99 g (86% of theory).

MS (ES+): m/z (%) = 213 $(M+H^+)$ (100).

HPLC (method 4): R_t = 0.41 min.

In the same way it is possible, from the corresponding *tert*-butoxycarbonylamino derivatives, by treatment with hydrochloric acid in dioxane, to prepare the following amines in the form of their hydrochlorides and to react them further directly:

Example	Structure	MW	MS
12A		226.28	MS (ES+), m/z (%): 227 $(M+H)^+$ (80)
13A		226.28	MS (ES+), m/z (%): 227 $(M+H)^+$ (100)
14A		226.28	
15A		252.32	
16A		238.29	

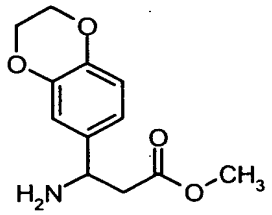
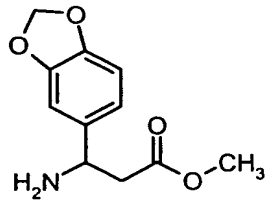
General instructions B: Preparation of the beta-amino acid methyl esters

The beta-amino acid [synthesis according to instructions known from the literature (e.g., S. Rault, P. Dallemagne, M. Robba, *Bull. Soc. Chim. Fr.*, 1987, 1079-1083; L. Lázár, T. Martinek, G. Bernáth, F. Fülöp, *Synth. Comm.*, 1998, 28, 219-224)] is introduced in methanol (about 0.5 to 1.0 mol/l) and admixed dropwise at 0°C with 1.2 eq. of thionyl chloride. After the end of the addition the reaction mixture is stirred

at room temperature overnight and then concentrated. The residue is dissolved in a little methanol and the product is precipitated with diethyl ether. The solid is filtered off with suction, washed repeatedly with diethyl ether and dried under reduced pressure.

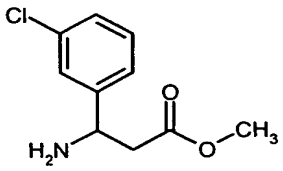
Alternatively the workup may take place as follows: following evaporation to dryness, the residue is taken up in water and washed twice with ethyl acetate. The organic phase is discarded and the aqueous phase is neutralized with saturated sodium hydrogen carbonate solution and again extracted three times with ethyl acetate. The organic phases of the final extraction are dried over sodium sulfate or magnesium sulfate, decanted and evaporated to dryness.

In accordance with general instructions B it is possible to obtain the following compounds:

Example	Structure	MW	MS
17A		237.25	MS (ES+), m/z (%): 238 $(M+H)^+$
18A		223.23	MS (ES+), m/z (%): 224 $(M+H)^+$

Example 19A

Methyl 3-amino-3-(3-chlorophenyl)propionate



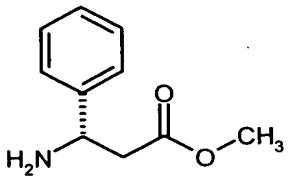
Methanol (110 ml) is cooled to–10°C and slowly admixed with thionyl chloride (12.0 g, 101.2 mmol). 3-Amino-3-(3-chlorophenyl)propionic acid (10.1 g, 50.6 mmol) is added and the mixture is stirred at room temperature overnight. The solution is concentrated to a high extent, under reduced pressure, and partitioned between ethyl acetate (100 ml) and saturated sodium hydrogen carbonate solution (200 ml). The pH of the aqueous phase is above 7. The aqueous phase is again extracted twice with ethyl acetate (100 ml). The combined ethyl acetate phases are dried over sodium sulfate, filtered and concentrated.

Yield: 9.7 g (87%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37 (s, 1 H), 7.30-7.20 (m, 3 H), 4.40 (t, 1 H), 3.68 (s, 3 H), 2.67-2.60 (m, 2 H).

Example 20A

Methyl (*S*)-3-amino-3-phenylpropionate



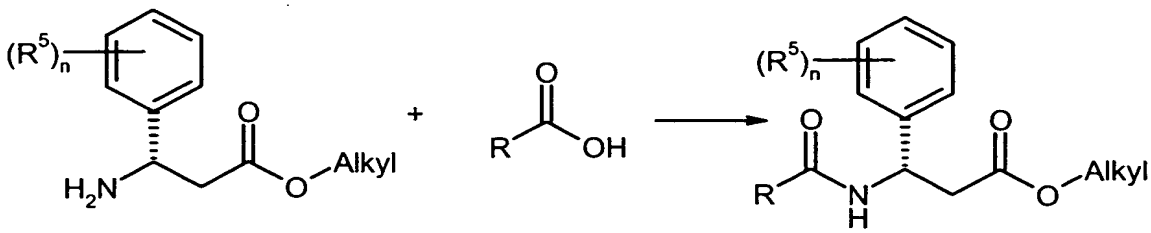
2.3 g (11.65 mmol) of (*S*)-3-amino-3-phenylpropionic acid are introduced in 100 ml of methanol and admixed with a catalytic amount of concentrated sulfuric acid (0.02 eq.). The reaction mixture is heated at reflux for 24 h and then concentrated. The crude product can be used without further purification in the next stage.

Yield: 2.7 g (65%).

^{1}H NMR (300 MHz, d_6-DMSO): δ = 8.50 (s, 2 H), 7.52-7.37 (m, 5 H), 4.61 (t, 1 H), 3.58 (s, 3 H), 3.13 (dd, 1 H), 2.98 (dd, 1 H).

MS (ES+): m/z (%) = 180 $(M+H)^+$ (100).

General instructions C: Reaction of 3-amino-3-phenylpropionic acid alkyl esters with carboxylic acids



The carboxylic acid (1.3 – 1.5 eq.) is introduced in dichloromethane (about 0.1 mol/l) at 0°C and admixed with 1.3 – 1.5 eq. of HATU. This mixture is admixed first with a solution of the 3-amino-3-phenylpropionic acid alkyl ester (1 eq.) in a 1:1 mixture of dichloromethane and N,N-dimethylformamide (about 0.1 mol/l) and subsequently dropwise, over a period of 1 h, with a solution of diisopropylethylamine (3.5 eq) in a 1:1 mixture of dichloromethane and N,N-dimethylformamide (about 1 mol/l). The mixture is stirred at 0°C for 30 minutes and then at room temperature overnight. The reaction mixture is then concentrated and purified by means of RP-HPLC (mobile phase: water-acetonitrile, gradient).

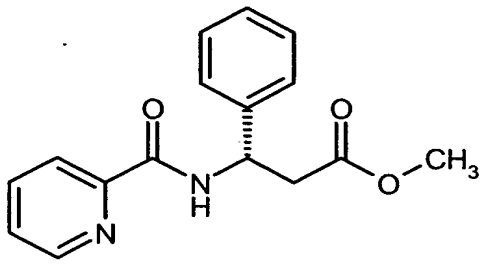
Alternatively the reaction may also take place by the following method:

A solution of the 3-aminopropionic acid alkyl ester (1 eq.) in absolute dichloromethane or a mixture (5:1 to 1:1) of absolute dichloromethane and N,N-dimethylformamide (about 0.1 to 0.3 mol/l) is admixed with the carboxylic acid derivative (1.1 - 1.5 eq.), triethylamine (3 eq.), HOBt (3 eq.) and finally 1.2 eq. of EDC. The reaction mixture is stirred at room temperature (2 h to overnight), before being concentrated under reduced pressure. The residue is taken up in ethyl acetate or dichloromethane and the organic phase is washed with water, saturated sodium hydrogencarbonate solution and saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. The product can be purified by chromatography on silica gel (mobile phases: mixtures of cyclohexane/ethyl acetate or mixtures of dichloromethane and ethanol) or by RP-HPLC (mobile phases:

variable gradients of water and acetonitrile), or alternatively by a combination of both methods.

Example 21A

Methyl (3*S*)-3-phenyl-3-[(2-pyridinylcarbonyl)amino]propionate



Synthesis in accordance with general instructions C.

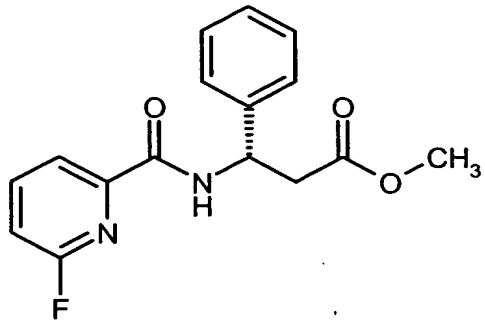
^{1}H NMR (300 MHz, d_6-DMSO): δ = 9.37 (d, 1 H), 8.67 (d, 1 H), 8.05-7.95 (m, 2 H), 7.66-7.57 (m, 1 H), 7.48-7.19 (m, 5 H), 5.49 (br. q, 1 H), 3.55 (s, 3 H), 3.19 (dd, 1 H), 2.96 (dd, 1 H).

MS (ES+): m/z (%) = 285 $(M+H)^+$ (35).

HPLC (method 5): R_t = 3.63 min.

Example 22A

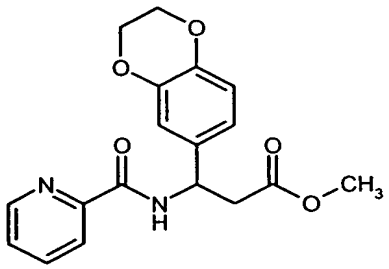
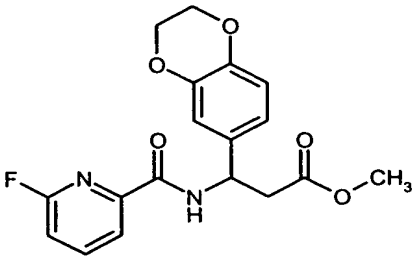
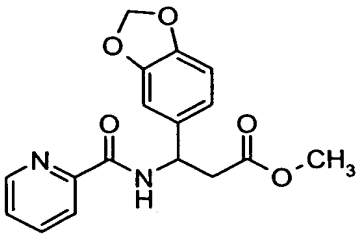
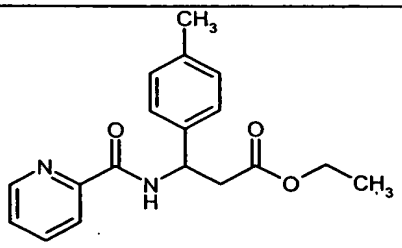
Methyl (3*S*)-3-{[(6-fluoro-2-pyridinyl)carbonyl]amino}-3-phenylpropionate



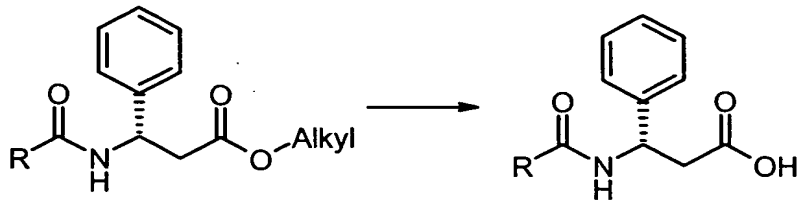
Synthesis in accordance with general instructions C.

^{1}H NMR (300 MHz, d_6-DMSO): δ = 9.23 (d, 1 H), 8.21-8.15 (m, 1 H), 7.96-7.92 (m, 1 H), 7.45-7.20 (m, 6 H), 5.46 (q, 1 H), 3.55 (s, 3 H), 3.18 (dd, 1 H), 2.96 (dd, 1 H).
MS (ES+): m/z (%) = 325 $(M+Na)^+$ (60).
HPLC (method 14): R_t = 4.35 min.

In accordance with general instructions C it is possible to obtain the following compounds:

Example	Structure	MW	MS
23A		342.35	MS (ES+), m/z (%): 343 $(M+H)^+$
24A		360.34	MS (ES+), m/z (%): 361 $(M+H)^+$
25A		328.32	MS (ES+), m/z (%): 329 $(M+H)^+$
26A		312.37	MS (ES+), m/z (%): 313 $(M+H)^+$

General instructions D: Hydrolysis of the propionic acid alkyl esters



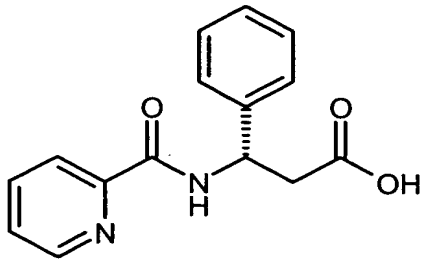
The propionic acid alkyl ester is introduced to a vessel in a 3:1 mixture of ethanol and water (about 0.1 – 0.15 mol/l) and 5 eq. of 40% strength sodium hydroxide solution are added. The reaction mixture is stirred at room temperature for 24 h, acidified with dilute hydrochloric acid (to a pH of about 3) and concentrated. The residue is taken up in ethyl acetate and washed with saturated aqueous sodium chloride solution. The organic phase is dried over magnesium sulfate, filtered and concentrated. The product obtained can be used without further purification in the next stage.

An alternative option is to use the following method:

The propionic acid alkyl ester is introduced to a vessel in a 1:1 mixture of dioxane and water (about 0.1 – 0.15 mol/l) and 3 eq. of a solution of potassium hydroxide in methanol (100 mg/ml) are added. The reaction mixture is stirred at room temperature for 2 h and then concentrated. The residue is taken up in water and acidified with dilute hydrochloric acid. The aqueous phase is extracted three times with a 1:1 mixture of dichloromethane and ethyl acetate. The combined organic phases are dried over sodium sulfate, filtered and concentrated. The product obtained can be used without further purification in the next stage.

Example 27A

(3*S*)-3-Phenyl-3-[(2-pyridinylcarbonyl)amino]propionic acid



Synthesis in accordance with general instructions D.

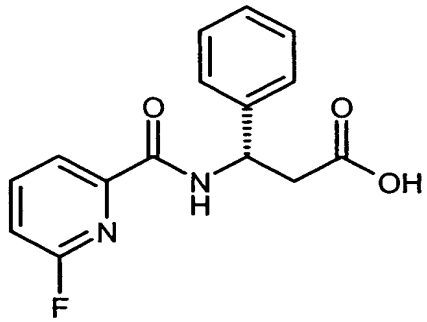
^{1}H NMR (300 MHz, d_6-DMSO): δ = 12.22 (s, 1 H), 9.30 (d, 1 H), 8.68 (d, 1 H), 8.05-7.95 (m, 2 H), 7.66-7.58 (m, 1 H), 7.46-7.19 (m, 5 H), 5.45 (q, 1 H), 3.04 (dd, 1 H), 2.87 (dd, 1 H).

MS (ES-): m/z (%) = 269 $(M-H)^-$ (100).

HPLC (method 5): R_t = 3.12 min.

Example 28A

(3*S*)-3-{[(6-Fluoro-2-pyridinyl)carbonyl]amino}-3-phenylpropionic acid

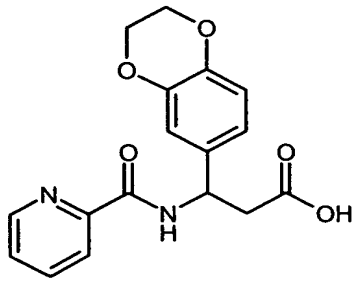
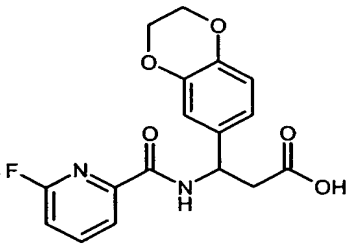
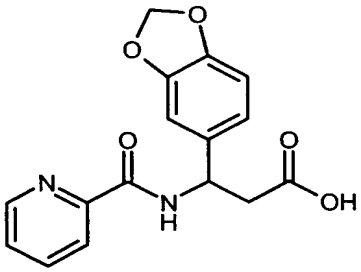
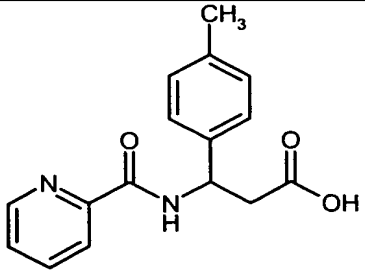


Synthesis in accordance with general instructions D.

MS (ES-): m/z (%) = 287 $(M-H)^-$ (100).

HPLC (method 13): R_t = 3.61 min.

In accordance with general instructions D it is possible to obtain the following compounds:

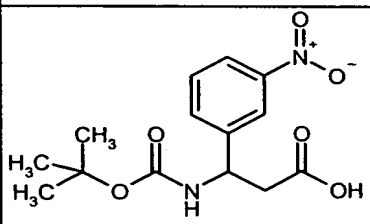
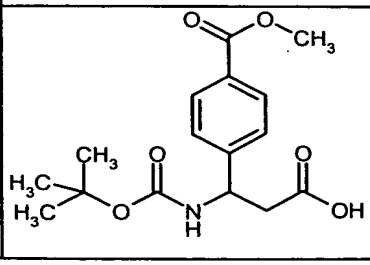
Example	Structure	MW	MS	HPLC
29A		328.32	MS (ES+), m/z (%): 329 $(M+H)^+$	
30A		346.31	MS (ES-), m/z (%): 345 $(M-H)^-$	HPLC (method 9): R_t = 3.69 min
31A		314.3	MS (ES+), m/z (%): 315 $(M+H)^+$	
32A		284.31	MS (ES+), m/z (%): 285 $(M+H)^+$	HPLC (method 9): R_t = 3.82 min

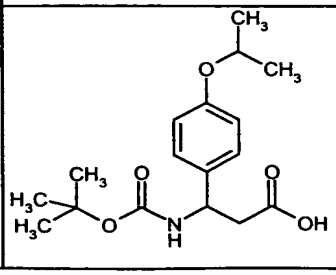
The propionic acid derivatives obtained in this way can be reacted in accordance with the instructions described below (reaction of 3-[2-aminoalkanoyl]-2,5-pyrrolidinedione hydrochloride derivatives with carboxylic acid derivatives).

General instructions E: Preparation of N-*tert*-butoxycarbonyl-protected beta-amino acids

The beta-amino acid (1 eq.) [synthesis in accordance with instructions known from the literature (e.g., S. Rault, P. Dallemagne, M. Robba, *Bull. Soc. Chim. Fr.*, 1987, 1079-1083; L. Lázár, T. Martinek, G. Bernáth, F. Fülöp, *Synth. Comm.*, 1998, 28, 219-224)] is introduced in water (concentration about 0.3 – 1 mol/l) and admixed with triethylamine (1.5 – 3 eq.). Then a solution of 2-(*tert*-butoxycarbonyloximino)-phenylacetonitrile (1.1 eq.) in dioxane (0.3 – 1 mol/l) is added. The reaction mixture is stirred at room temperature for 3 h, diluted with water and washed with diethyl ether. The aqueous phase is acidified with 5% strength citric acid (to a pH of about 2) and extracted three times with ethyl acetate. The combined organic phases are washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. The crude product can if desired be recrystallized from ethyl acetate/n-hexane.

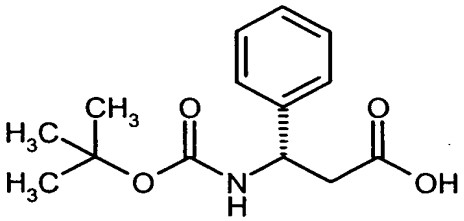
In accordance with general instructions E it is possible to obtain the following compounds:

Example	Structure	MW	MS	HPLC
33A		310.3	MS (ES+), m/z (%): 311 $(M+H)^+$	HPLC (method 8): R_t = 3.87 min
34A		323.34	MS (ES+), m/z (%): 324 $(M+H)^+$	HPLC (method 8): R_t = 2.39 min

Example	Structure	MW	MS	HPLC
35A		323.39	MS (ES-), m/z (%): 322 $(M-H)^-$	HPLC (method 14): R_t = 4.35 min

Example 36A

(3*S*)-3-[(tert-Butoxycarbonyl)amino]-3-phenylpropionic acid

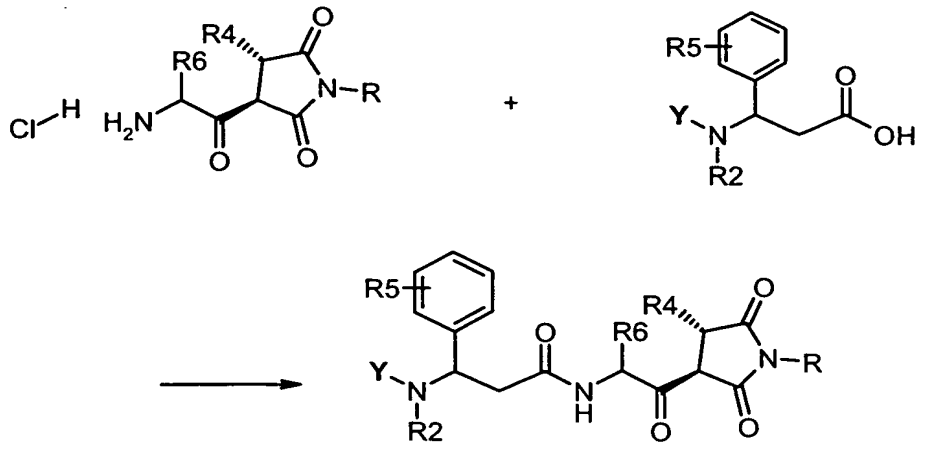


2.82 g (17 mmol) of (*S*)-3-amino-3-phenylpropionic acid are slurred in 60 ml of dioxane and at 0°C 4.1 g (18.8 mmol) of di-tert-butyl dicarbonate (Boc anhydride) and 43 ml of a 1N sodium hydroxide solution in water are added to the slurry. The reaction mixture is stirred at 0°C for 30 minutes and then at room temperature for 3 h. Subsequently the reaction mixture is concentrated and the residue is taken up in methylene chloride. The organic phase is washed with 1N hydrochloric acid and saturated sodium chloride solution, dried over magnesium sulfate and concentrated. The crude product (3.12 g) can be reacted further without additional purification.

MS (ES-): m/z (%) = 264 $(M-H)^-$ (100).

HPLC (method 14): R_t = 3.89 min.

General instructions F: Acylation of 3-[2-aminoalkanoyl]-2,5-pyrrolidinedione hydrochloride derivatives with carboxylic acid derivatives



A solution of carboxylic acid derivative (1.2 – 1.5 eq.) in absolute dichloromethane or a mixture (5:1 to 1:1) of absolute dichloromethane and N,N-dimethylformamide (about 0.1 to 0.3 mol/l) is admixed at 0°C first with an equimolar amount of HATU and then with the 3-[2-aminoalkanoyl]-2,5-pyrrolidinedione hydrochloride derivative (1 eq., optionally as a solution in N,N-dimethylformamide or dichloromethane/N,N-dimethylformamide mixtures). Subsequently at 0°C a solution of 2.5 - 3.5 eq. of diisopropylethylamine in a 1:1 mixture of absolute dichloromethane and N,N-dimethylformamide (0.2 – 1 mol/l) is added dropwise over a period of 1 h. After the end of the addition the reaction mixture is stirred at 0°C for 30 minutes more and then at room temperature overnight, before being concentrated under reduced pressure. The product can be obtained by chromatography on silica gel (mobile phases: mixtures of cyclohexane/ethyl acetate or mixtures of dichloromethane and ethanol) or by RP-HPLC (mobile phases: variable gradients of water and acetonitrile), or alternatively by a combination of both methods.

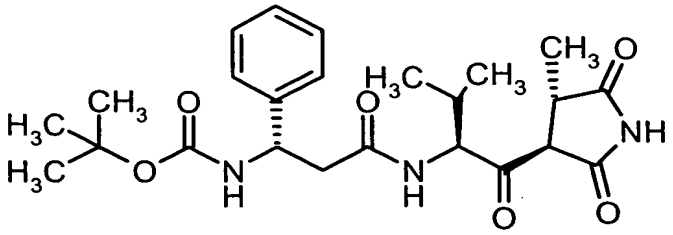
Alternatively the reaction may also take place by the following method:

A solution of the 3-[2-aminoalkanoyl]-2,5-pyrrolidinedione hydrochloride derivative (1 eq.) in absolute dichloromethane or a mixture (5:1 to 1:1) of absolute

dichloromethane and N,N-dimethylformamide (about 0.1 to 0.3 mol/l) is admixed with the carboxylic acid derivative (1.1 – 1.5 eq.), triethylamine (3 eq.), HOBt (3 eq.) and finally 1.2 eq. of EDC. The reaction mixture is stirred at room temperature (2 h to overnight) before being concentrated under reduced pressure. The residue is taken up in ethyl acetate or dichloromethane and the organic phase is washed with water, saturated sodium hydrogencarbonate solution and saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. The product can be purified by chromatography on silica gel (mobile phases: mixtures of cyclohexane/ethyl acetate or mixtures of dichloromethane and ethanol) or by RP-HPLC (mobile phases: variable gradients of water and acetonitrile), or alternatively by a combination of both methods.

Example 37A

tert-Butyl ((*S*)-2-{(*S*)-2-methyl-1-[1-((3*R*,4*S*)-4-methyl-2,5-dioxo-pyrrolidin-3-yl)-methanoyl]-propylcarbamoyl}-1-phenylethyl)carbamate



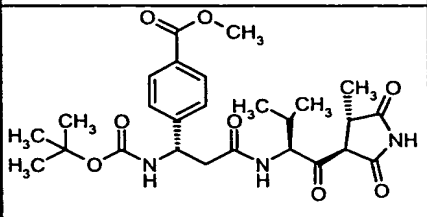
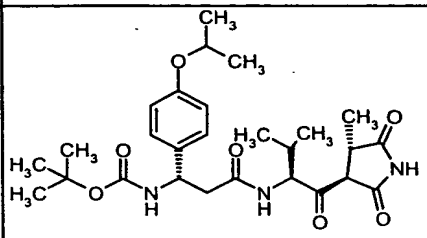
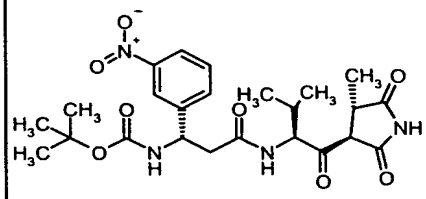
Synthesis in accordance with general instructions F.

^{1}H-NMR (400 MHz, d_6-DMSO): δ = 11.45 (s, 1 H), 7.98 (d, 1 H), 7.31-7.24 (m, 5 H), 7.20 (br. s, 1 H), 4.88-4.82 (br. s, 1 H), 4.69 (br. s, 1 H), 3.98 (d, 1 H), 2.95-2.89 (m, 1 H), 2.77-2.69 (m, 1 H), 2.51-2.44 (m, 1 H), 2.35-2.29 (m, 1 H), 1.10 (d, 3 H), 0.85 (d, 3 H), 0.78 (d, 3 H).

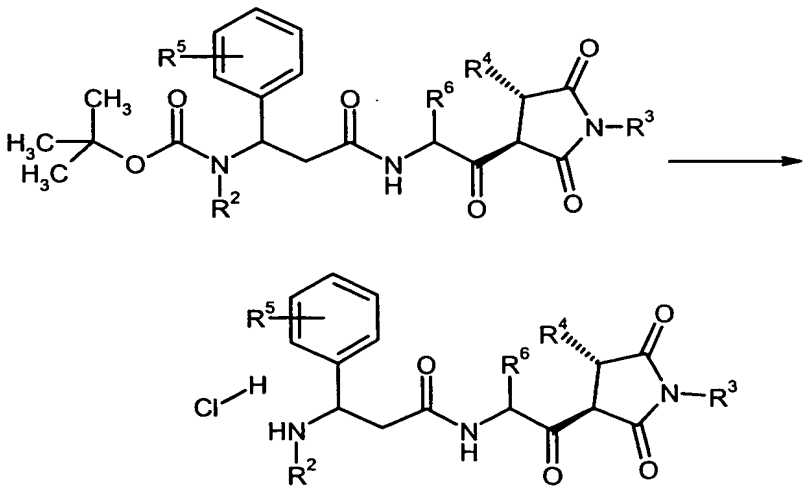
MS (ES+): m/z (%) = 460 ($M+H^+$) (100).

HPLC (method 6): R_t = 3.90 min.

In accordance with general instructions F it is possible to obtain the following compounds:

Example	Structure	MW	MS	HPLC
38A		517.58	MS (ES+), m/z (%): 518 $(M+H)^+$	HPLC (method 8): R_t = 2.60 min
39A		517.62	MS (ES+), m/z (%): 518 $(M+H)^+$	HPLC (method 14): R_t = 4.42 min
40A		504.54	MS (ES-), m/z (%): 503 $(M-H)^-$	HPLC (method 6): R_t = 3.99 min

General instructions G: Deblocking of Boc-protected derivatives

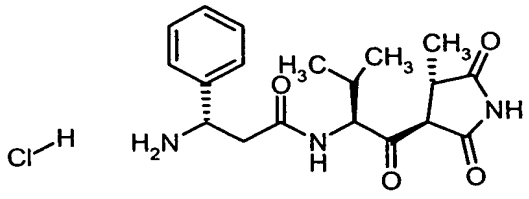


5

The *tert*-butyloxycarbonyl (BOC) protected amine derivative (optionally as a solution in dioxane) is admixed at 0°C or room temperature with 4N hydrochloric acid solution in 1,4-dioxane (about 0.1 mol/l) and stirred at room temperature for 2 to 24 h before being concentrated under reduced pressure. The residue can be reacted further without additional purification or if desired is treated with dichloromethane and diethyl ether. The precipitated crystals are filtered off with suction and dried under a high vacuum. This gives the product as the hydrochloride.

Example 41A

(*S*)-3-Amino-{(*S*)-2-methyl-1-[1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-methanoyl]-propyl}-3-phenylpropionamide hydrochloride



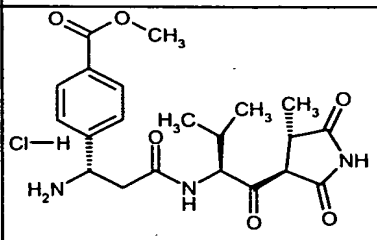
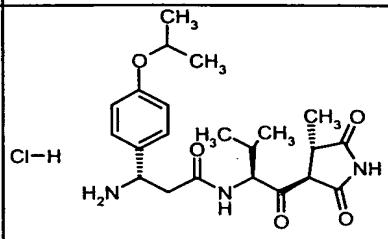
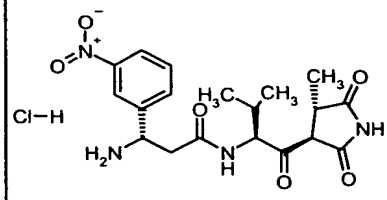
Synthesis in accordance with general instructions G.

^{1}H-NMR (200 MHz, d_6-DMSO): δ = 11.49 (br. s, 1 H), 8.5 (br. s, about 3 H), 7.54-7.32 (m, 5 H), 4.69-4.55 (m, 2 H), 3.89 (d, 1 H), 3.06-2.80 (m, 3 H), 2.39-2.25 (m, 1 H), 1.01 (d, 3 H), 0.81 (d, 3 H), 0.75 (d, 3 H).

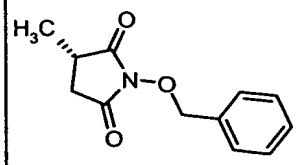
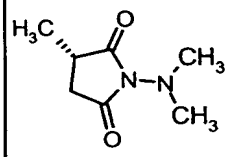
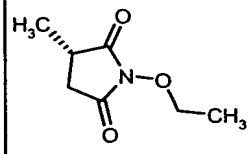
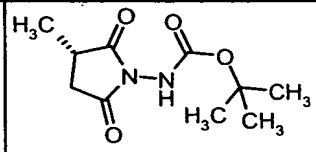
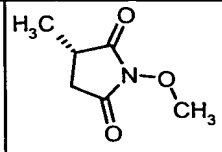
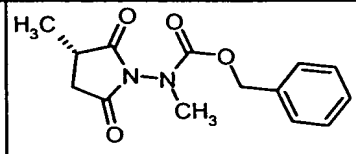
MS (ES+): m/z (%) = 360 $(M+H)^+$ (100).

HPLC (method 4): R_t = 1.44 min.

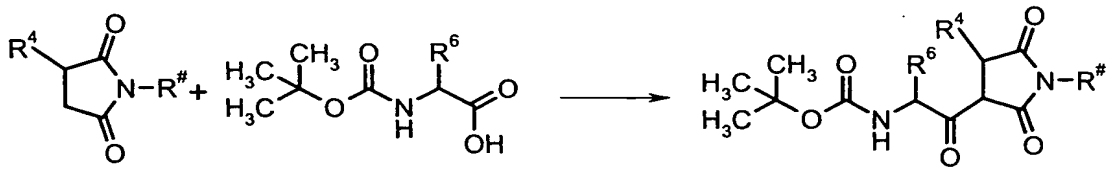
In accordance with general instructions G it is possible to obtain the following compounds:

Example	Structure	MW	MS	HPLC
42A		417.46	MS (ES-), m/z (%): 416 $(M-H)^-$	HPLC (method 5): R_t = 2.23 min
43A		417.51	MS (ES-), m/z (%): 416 $(M-H)^-$	HPLC (method 9): R_t = 2.97 min
44A		404.42		

In the same way as for Example 1A the following compounds are obtained by reacting (3*S*)-3-methyldihydro-2,5-furandione with the corresponding primary amines, hydroxylamine derivatives or hydrazine derivatives. The crude products can be purified by RP-HPLC (mobile phase: water-acetonitrile, gradient).

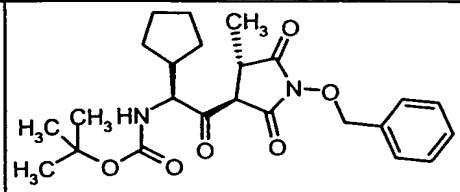
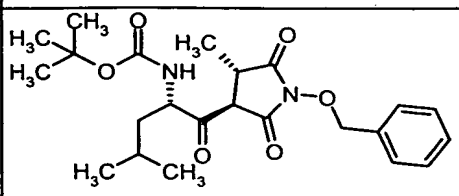
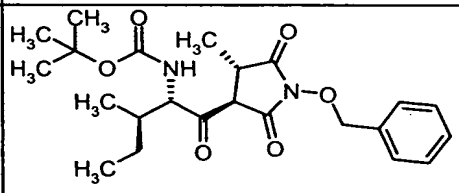
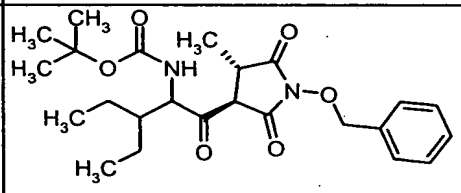
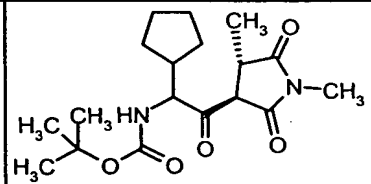
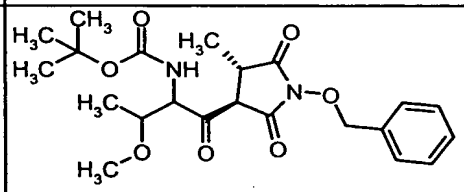
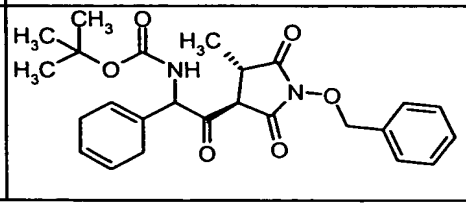
Example	Structure	MW	MS	HPLC
45A		219.24		HPLC (method 6): R_t = 3.37 min
46A		156.18	MS (ESI+), m/z: 157 $(M+H)^+$	HPLC (method 19): R_t = 2.62 min
47A		157.17	MS (DCI), m/z: 175 $(M+NH_4)^+$	HPLC (method 20): R_t = 1.70 min
48A		228.25	MS (DCI), m/z: 246 $(M+NH_4)^+$	HPLC (method 20): R_t = 2.09 min
49A		143.14	MS (ESI+), m/z: 144 $(M+H)^+$	
50A		276.29	MS (DCI), m/z: 294 $(M+NH_4)^+$	HPLC (method 21): R_t = 2.80 min

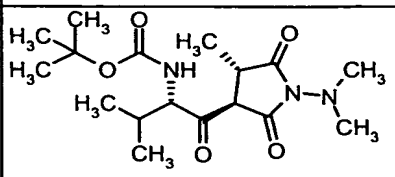
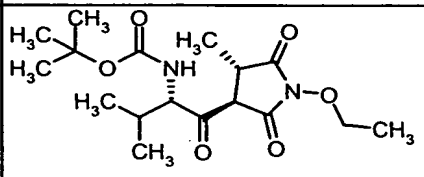
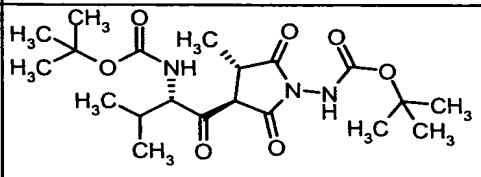
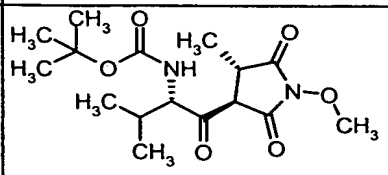
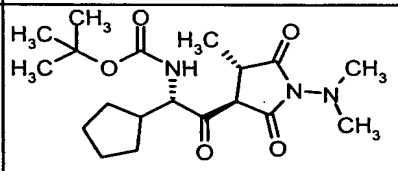
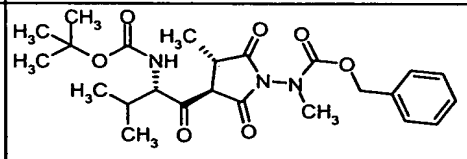
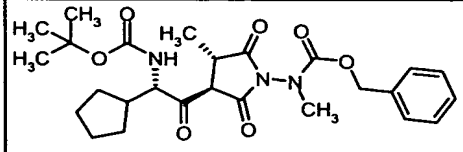
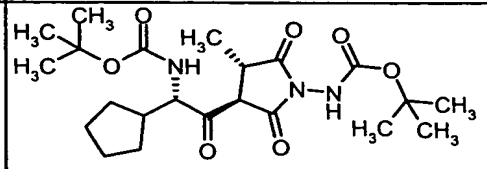
General instructions J: Reaction of N-*tert*-butoxycarbonyl-protected amino acids with 2,5-pyrrolidinedione derivatives

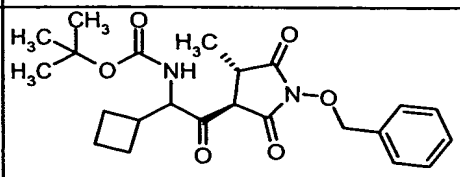


The N-*tert*-butoxycarbonyl-protected amino acid (1 eq.) and N,N-carbonyldiimidazole (1.1 eq.) are stirred in tetrahydrofuran (about 0.1 – 1 mol/l) at room temperature for 2 h. The 2,5-pyrrolidinedione (1 eq.) is then added to this mixture and the total mixture is added dropwise over the course of 30 minutes to a 1 molar solution of lithium hexamethyldisilazide (2 eq.) in THF, which is cooled at -65°C. After the end of the addition stirring is continued at –65°C for 15 minutes more, and then saturated aqueous ammonium chloride solution is added. After the reaction mixture has been warmed to room temperature it is diluted with diethyl ether and the organic phase is washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and subsequently concentrated. The crude product is purified by RP-HPLC (mobile phase: water-acetonitrile, gradient).

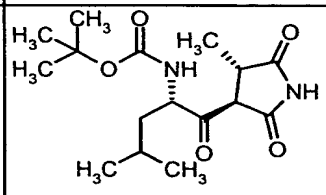
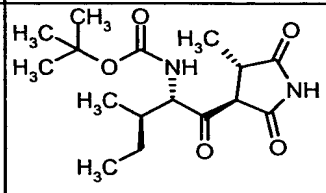
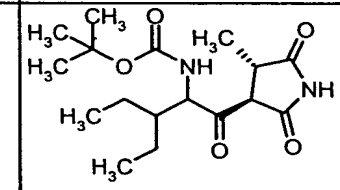
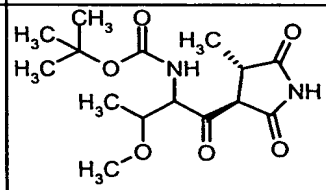
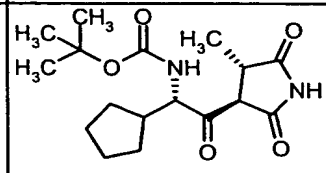
In accordance with general instructions J it is possible by reacting the corresponding N-*tert*-butoxycarbonyl-protected amino acids (for the preparation of non-natural alpha-amino acids see, for example, A. A. Cordi *et al.*, *J. Med. Chem.* 2001, *44*, 787-805; K. Mai, G. Patil, *Tetrahedron Lett.* 1984, *25*, 4583-4586; N. A. Hassan, E. Bayer, J. C. Jochims, *J. Chem. Soc., Perkin Trans. 1* 1998, 3747–3757; for the *tert*-butoxycarbonyl protection see, e.g., T. W. Greene, P. G. M. Wuts, Protective Groups in Organic Synthesis, 3rd Edt. 1999, J. Wiley & Sons, Inc.) with 2,5-pyrrolidinediones to obtain the following derivatives:

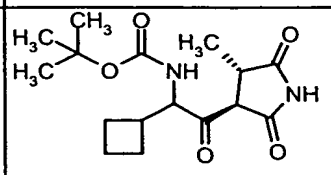
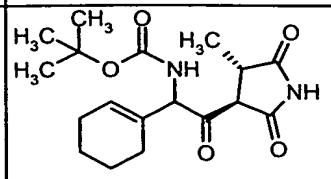
Example	Structure	MW	MS	HPLC
51A		444.53	MS (ES-), m/z: 443 $(M-H)^-$	HPLC (method 18): R_t = 4.11 min
52A		432.51	MS (ES-), m/z: 431 $(M-H)^-$	HPLC (method 6): R_t = 4.88 min
53A		432.51	MS (ES-), m/z: 431 $(M-H)^-$	HPLC (method 13): R_t = 5.08 min
54A		446.54	MS (ES-), m/z: 445 $(M-H)^-$	HPLC (method 17): R_t = 4.42 min
55A		352.43	MS (ES-), m/z: 351 $(M-H)^-$	HPLC (method 14): R_t = 4.61 min
56A		434.49	MS (ES-), m/z: 433 $(M-H)^-$	HPLC (method 17): R_t = 3.98 min
57A		454.52	MS (ES-), m/z: 453 $(M-H)^-$	HPLC (method 22): R_t = 4.41 min

Example	Structure	MW	MS	HPLC
58A		355.43	MS (ES+), m/z: 378 $(M+Na)^+$	HPLC (method 19): R_t = 4.12 min
59A		356.42	MS (ES-), m/z: 355 $(M-H)^-$	HPLC (method 20): R_t = 3.64 min
60A		427.50	MS (ES-), m/z: 426 $(M-H)^-$	HPLC (method 20): R_t = 3.73 min
61A		342.39	MS (ES-), m/z: 341 $(M-H)^-$	HPLC (method 19): R_t = 4.18 min
62A		381.47	MS (ES-), m/z: 380 $(M-H)^-$	HPLC (method 21): R_t = 3.43 min
63A		475.54	MS (ES-), m/z: 474 $(M-H)^-$	HPLC (method 20): R_t = 3.91 min
64A		501.58	MS (ES-), m/z: 500 $(M-H)^-$	HPLC (method 21): R_t = 3.93 min
65A		453.53	MS (ES-), m/z: 452 $(M-H)^-$	HPLC (method 21): R_t = 3.61 min

Example	Structure	MW	MS	HPLC
66A		430.51	MS (ES+), m/z: 453 $(M+Na)^+$	HPLC (method 20): R_t = 4.32 min

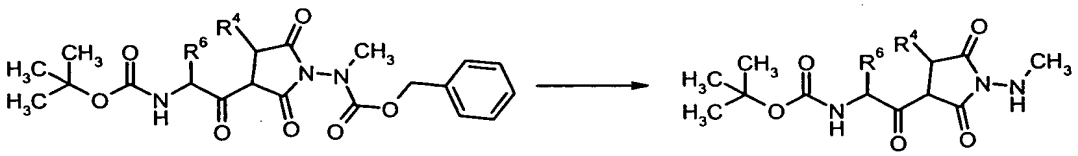
In accordance with general instructions A it is possible to obtain the following compounds:

Example	Structure	MW	MS	HPLC
67A		326.39	MS (ES-), m/z: 325 $(M-H)^-$	HPLC (method 5): R_t = 3.91 min
68A		326.39	MS (ES-), m/z: 325 $(M-H)^-$	HPLC (method 12): R_t = 2.88 min
69A		340.42	MS (ES-), m/z: 339 $(M-H)^-$	HPLC (method 17): R_t = 3.59 min
70A		328.26	MS (ES+), m/z: 351 $(M+Na)^+$	HPLC (method 20): R_t = 3.18 min
71A		338.40	MS (ES-), m/z: 337 $(M-H)^-$	HPLC (method 17): R_t = 3.57 min

Example	Structure	MW	MS	HPLC
72A		324.38	MS (ES-), m/z: 323 $(M-H)^-$	HPLC (method 19): R_t = 4.02 min
73A		350.41	MS (ES-), m/z: 349 $(M-H)^-$	HPLC (method 18): R_t = 3.66 min

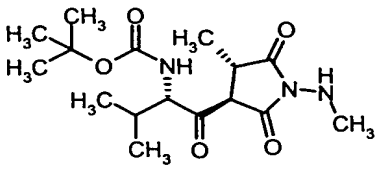
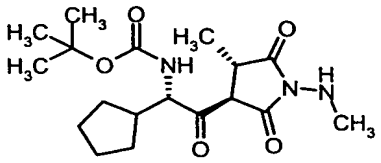
Compound 73A was formed in the course of the reaction of compound 57A.

General instructions K: Deblocking of benzyloxycarbonyl-protected hydrazine derivatives

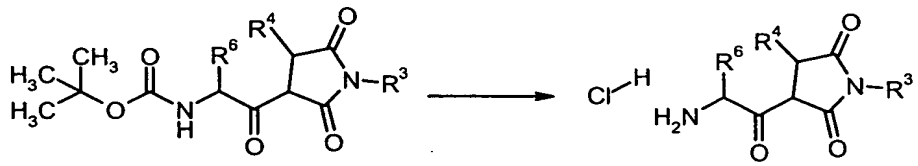


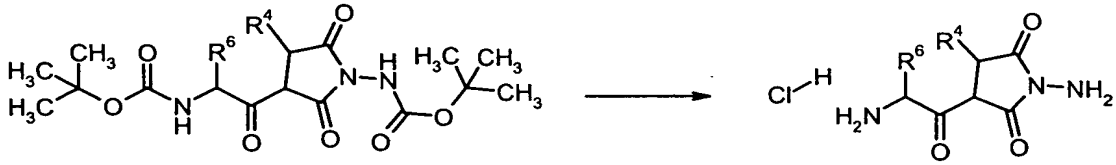
The benzyloxycarbonyl-protected hydrazine derivative (1 eq.) is dissolved in methanol or ethanol (about 0.05 mol/l), a catalytic amount of palladium-on-carbon (10%) is added and the mixture is stirred under a hydrogen atmosphere (atmospheric pressure) for 3 – 4 h. The reaction mixture is then filtered and concentrated. The crude product can be reacted without further purification.

In accordance with general instructions K is it possible to obtain the following compounds:

Example	Structure	MW	MS	HPLC
74A		341.41	MS (ES-), m/z: 340 $(M-H)^-$	HPLC (Methode 19): R_t = 4.00 min
75A		367.44	MS (ES-), m/z: 366 $(M-H)^-$	HPLC (Methode 20): R_t = 3.47 min

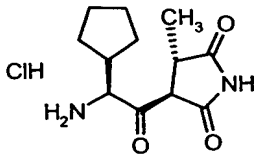
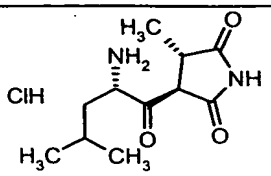
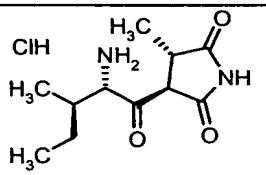
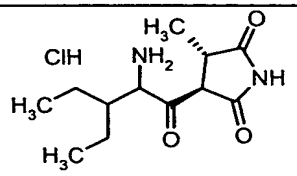
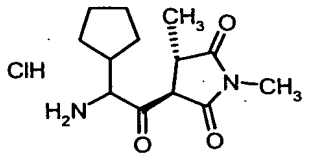
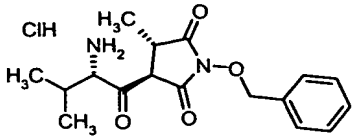
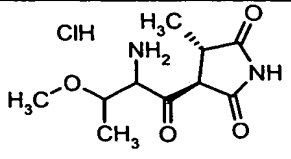
General instructions L: Deblocking of Boc-protected derivatives

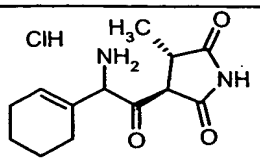
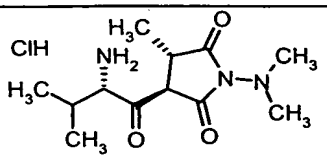
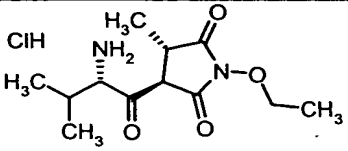
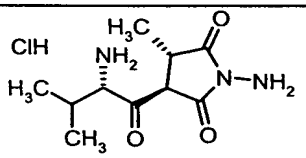
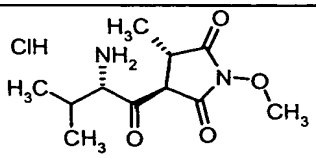
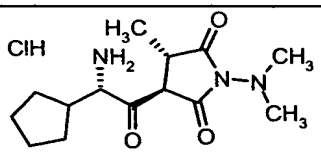
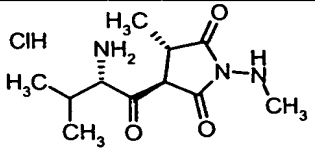
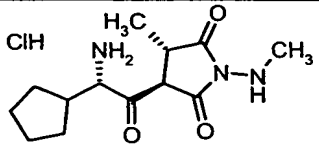


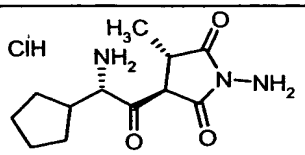
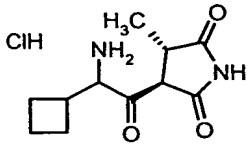


The *tert*-butyloxycarbonyl (BOC)-protected amine derivative (optionally as a solution in dioxane) is admixed with a 4N solution of hydrochloric acid in 1,4-dioxane (about 0.1 mol/l) and stirred at room temperature for 2-24 h before being concentrated under reduced pressure. The residue can be reacted further without additional purification or if desired is treated with dichloromethane and diethyl ether. The precipitated crystals are filtered off with suction and dried under a high vacuum. The product is obtained as the hydrochloride.

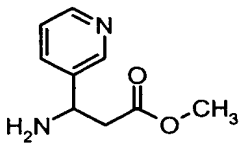
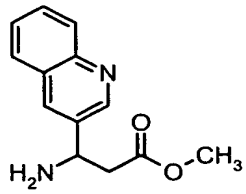
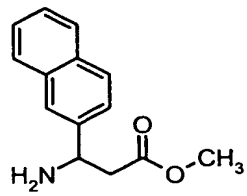
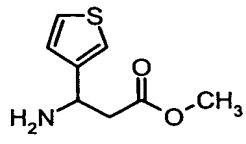
In accordance with general instruction L it is possible to obtain the following compounds:

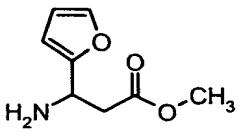
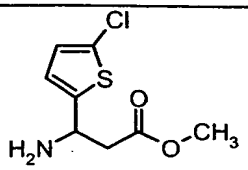
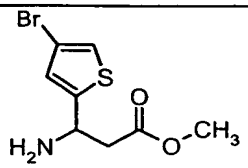
Ex-ample	Structure	MW
76A		238.29
77A		226.28
78A		226.28
79A		240.30
80A		252.32
81A		318.38
82A		228.25

Example	Structure	MW
83A		250.30
84A		255.32
85A		256.30
86A		227.27
87A		242.28
88A		281.36
89A		241.29
90A		267.33

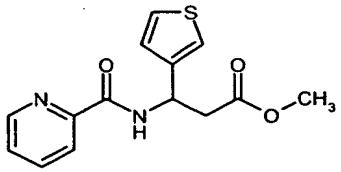
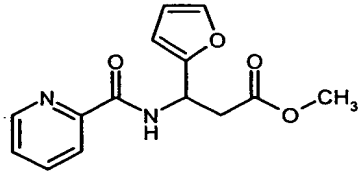
Ex-ample	Structure	MW
91A		253.30
92A		224.26

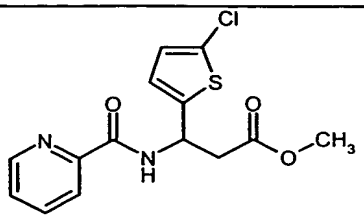
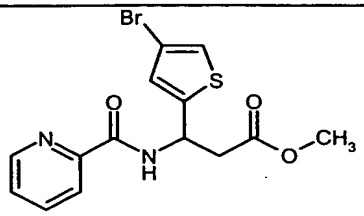
In accordance with general working instructions B it is possible to prepare the following compounds:

Ex-ample	Structure	MW	MS	HPLC
93A		180.2	MS (ES+), m/z: 180 $(M+H)^+$	
94A		230.3	MS (ES+), m/z: 231 $(M+H)^+$	HPLC (method 20): R_t = 1.70 min
95A		229.3	MS (ES+), m/z: 230 $(M+H)^+$	HPLC (method 19): R_t = 1.75 min
96A		185.3	MS (ES+), m/z: 186 $(M+H)^+$	

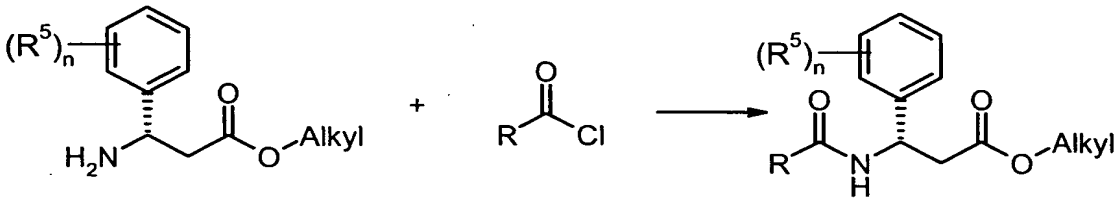
Example	Structure	MW	MS	HPLC
97A		169.2	MS (ES+), m/z: 170 $(M+H)^+$	
98A		219.69	MS (ES+), m/z: 220 $(M+H)^+$	
99A		264.14	MS (ES+), m/z: 264 $(M+H)^+$	

In accordance with general instructions C it is possible to obtain the following compounds:

Example	Structure	MW	MS
100A		290.34	MS (ES+), m/z (%): 291 $(M+H)^+$
101A		274.28	MS (ES+), m/z (%): 275 $(M+H)^+$

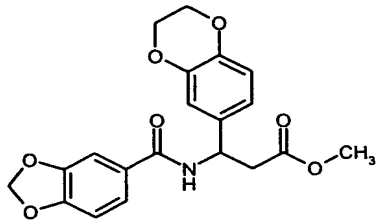
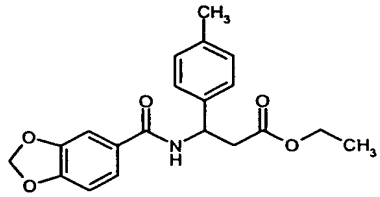
Ex-ample	Structure	MW	MS
102A		324.79	MS (ES+), m/z (%): 325 $(M+H)^+$
103A		369.24	MS (ES+), m/z (%): 369 $(M+H)^+$

General instructions M: Reaction of 3-aminopropionic acid alkyl esters with carbonyl chlorides

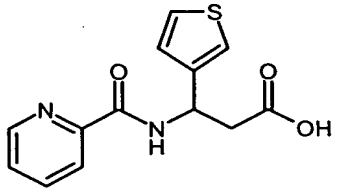
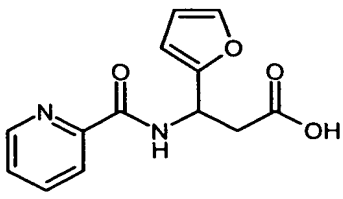


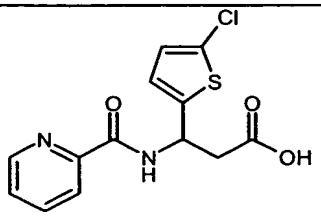
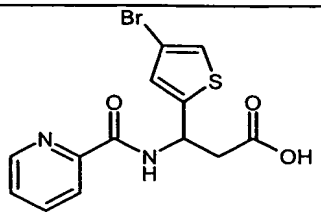
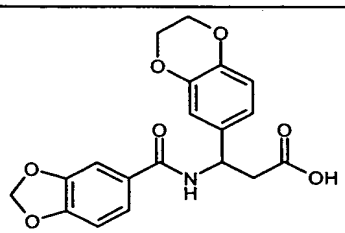
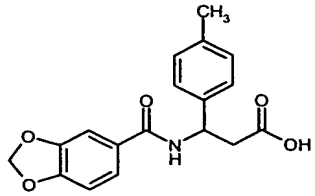
The 3-aminopropionic acid alkyl ester is introduced in dichloromethane (about 0.1-0.4 mol/l) at room temperature and 2-3 eq. of diisopropylethylamine and 1.2 eq. of the carbonyl chloride are added. The mixture is stirred at room temperature for 2-3 h. Then water is added to the reaction mixture and the organic phase is separated off, dried over sodium sulfate, filtered and concentrated. The residue can be recrystallized from dichloromethane and diethyl ether or purified by means of chromatography on silica gel (mobile phase: mixtures of dichloromethane and ethyl acetate).

In accordance with general instructions M it is possible to obtain the following compounds:

Example	Structure	MW	MS
104A		385.38	MS (ES+), m/z (%): 386 $(M+H)^+$
105A		355.39	MS (ES+), m/z (%): 356 $(M+H)^+$

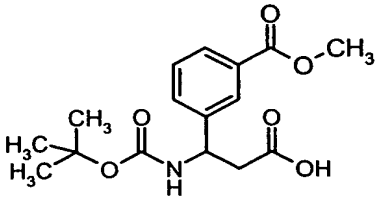
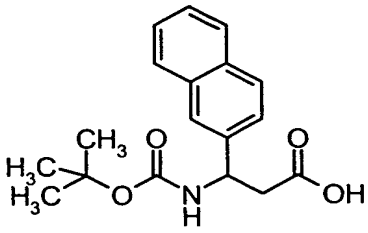
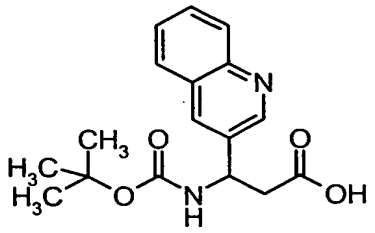
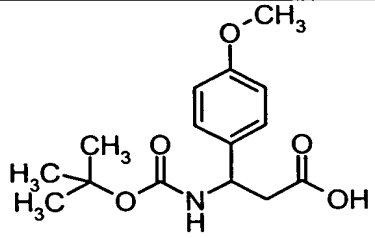
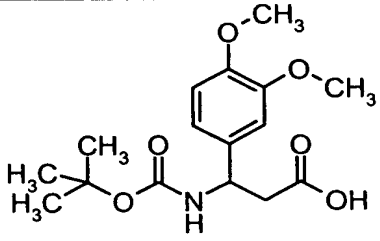
In accordance with general instructions D it is possible to obtain the following compounds:

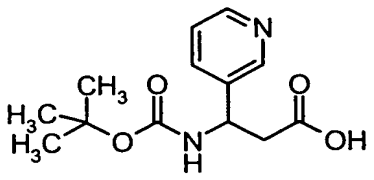
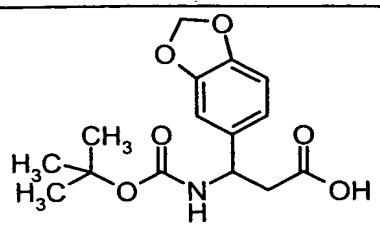
Example	Structure	MW	MS	HPLC
106A		276.32	MS (ES+), m/z (%): 277 $(M+H)^+$	HPLC (method 9): R_t = 3.55 min
107A		260.25	MS (ES+), m/z (%): 261 $(M+H)^+$	HPLC (method 9): R_t = 3.43 min

Example	Structure	MW	MS	HPLC
108A		310.76	MS (ES+), m/z (%): 311 $(M+H)^+$	HPLC (method 9): R_t = 3.92 min
109A		355.21	MS (ES+), m/z (%): 355 $(M+H)^+$	HPLC (method 9): R_t = 3.89 min
110A		371.35	MS (ES+), m/z (%): 372 $(M+H)^+$	HPLC (method 9): R_t = 3.64 min
111A		327.34	MS (ES+), m/z (%): 328 $(M+H)^+$	

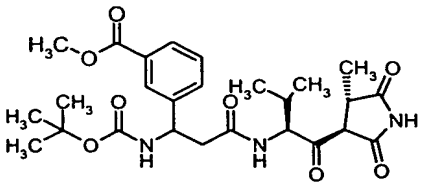
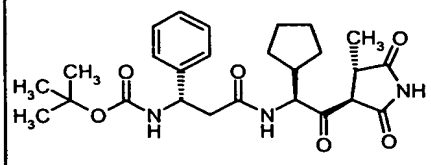
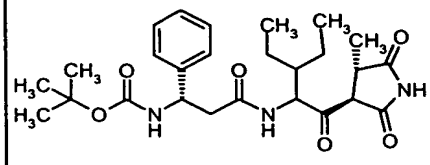
The propionic acid derivatives obtained in this way can be reacted in accordance with the general instructions F described below (acylation of 3-[2-aminoalkanoyl]-2,5-pyrrolidinedione hydrochloride derivatives with carboxylic acid derivatives).

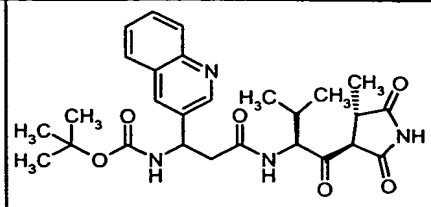
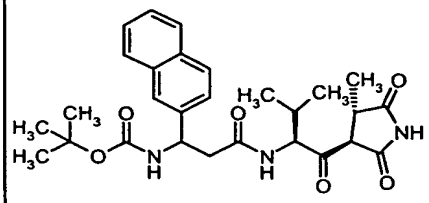
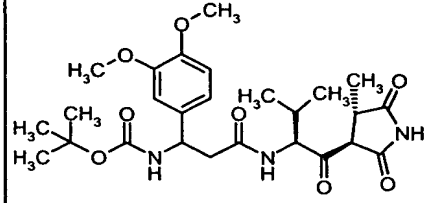
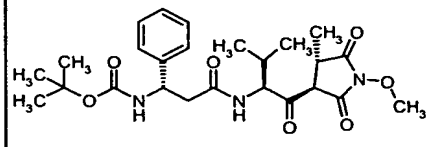
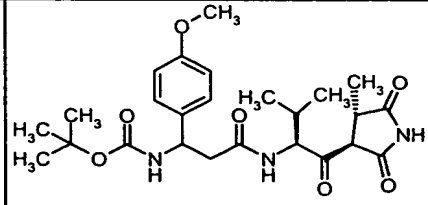
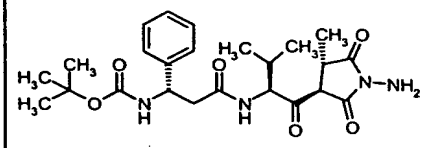
In accordance with general instructions E it is possible to obtain the following compounds:

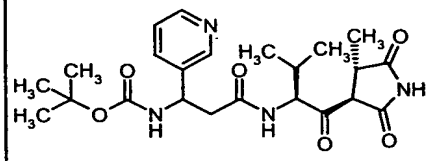
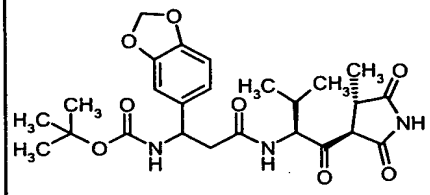
Example	Structure	MW	MS	HPLC
112A		323.35		HPLC (method 9): R_t = 3.96 min
113A		315.37	MS (ESI-), m/z: 314 $(M-H)^-$	HPLC (method 21): R_t = 3.21 min
114A		316.36	MS (ESI+), m/z: 317 $(M+H)^+$	HPLC (method 19): R_t = 3.47 min
115A		295.33	MS (ESI+), m/z: 296 $(M+H)^+$	HPLC (method 20): R_t = 3.00 min
116A		325.36		HPLC (method 9): R_t = 3.76 min

Example	Structure	MW	MS	HPLC
117A		266.30	MS (DCI), m/z: 167 $(M-100+H)^+$	HPLC (method 9): R_t = 1.92 min
118A		309.32	MS (ESI-), m/z: 308 $(M-H)^-$	HPLC (method 13): R_t = 3.69 min

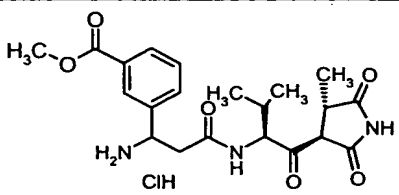
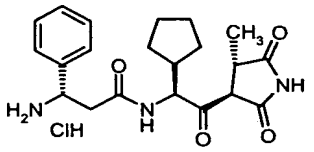
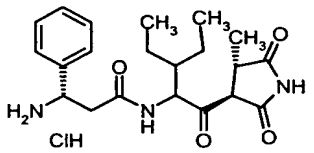
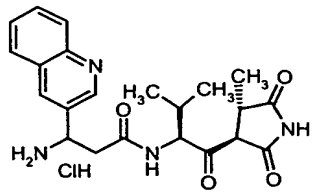
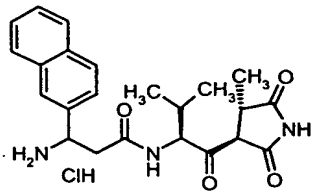
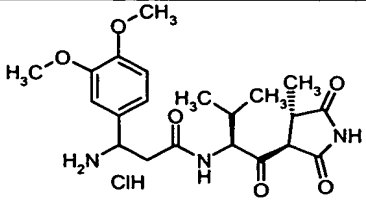
In accordance with general instructions F it is possible to obtain the following compounds:

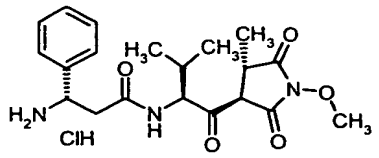
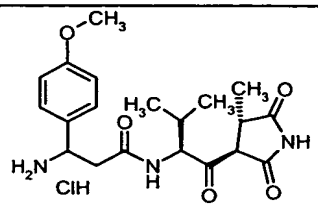
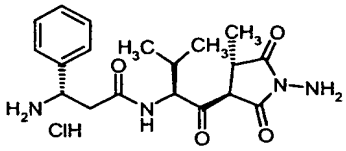
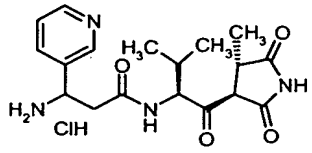
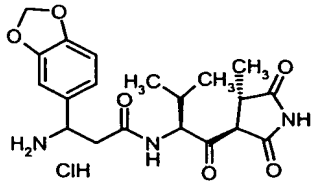
Example	Structure	MW	MS	HPLC
119A		517.58	MS (ESI+), m/z: 518 $(M+H)^+$	HPLC (method 16): R_t = 2.89 min
120A		485.58	MS (ESI-), m/z: 484 $(M-H)^-$	HPLC (method 20): R_t = 3.72 min
121A		487.59	MS (ESI+), m/z: 488 $(M+H)^+$	HPLC (method 17): R_t = 3.73 min

Example	Structure	MW	MS	HPLC
122A		510.59	MS (ESI-), m/z: 509 $(M-H)^-$	HPLC (method 19): R_t = 3.99 min
123A		509.61	MS (ESI-), m/z: 508 $(M-H)^-$	HPLC (method 20): R_t = 3.77 min
124A		519.60	MS (ESI-), m/z: 518 $(M-H)^-$	HPLC (method 18): R_t = 3.36 min
125A		489.57	MS (ESI-), m/z: 488 $(M-H)^-$	HPLC (method 19): R_t = 4.19 min
126A		489.57	MS (ESI-), m/z: 488 $(M-H)^-$	HPLC (method 20): R_t = 3.36 min
127A		474.56	MS (ESI-), m/z: 473 $(M-H)^-$	HPLC (method 19): R_t = 2.55 min

Example	Structure	MW	MS	HPLC
128A		460.53	MS (ESI+), m/z: 461 $(M+H)^+$	HPLC (method 5): R_t = 2.86 min
129A		503.56	MS (ESI+), m/z: 504 $(M+H)^+$	HPLC (method 14): R_t = 4.05 min

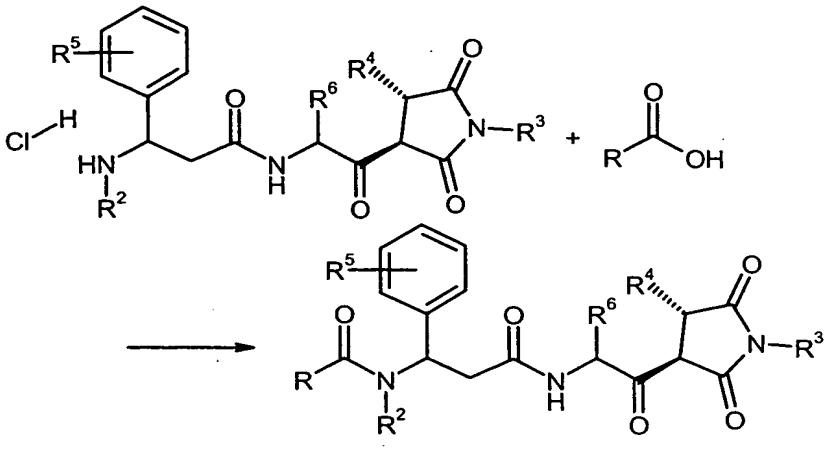
In accordance with general instructions G it is possible to obtain the following compounds:

Example	Structure	MW	MS	HPLC
130A		417.47		
131A		385.47	MS (ESI-), m/z: 384 $(M-H)^-$	HPLC (method 20): R_t = 1.90 min
132A		387.48		
133A		410.48		HPLC (method 9): R_t = 2.79 min
134A		409.49	MS (ESI-), m/z: 408 $(M-H)^-$	HPLC (method 20): R_t = 2.14 and 2.23 min
135A		419.48		HPLC (method 9): R_t = 2.80 min

Example	Structure	MW	MS	HPLC
136A		389.46	MS (ESI-), m/z: 388 $(M-H)^-$	HPLC (method 19): R_t = 3.17 min
137A		389.46		HPLC (method 9): R_t = 2.86 min
138A		374.44		
139A		360.42	MS (ESI+), m/z: 361 $(M+H)^+$	
140A		403.44	MS (ESI-), m/z: 402 $(M-H)^-$	HPLC (method 14): R_t = 2.40 min

Preparation examples:

General instructions H: Acylation of acylalkylamino substituted 3-[2-amino-alkanoyl]-2,5-pyrrolidinedione hydrochloride derivatives with carboxylic acid derivatives



A mixture of amine hydrochloride (1.0 eq.), carboxylic acid (1.2 to 1.3 eq.) and HATU (1.2 – 1.4 eq.) in solution in absolute N,N-dimethylformamide or in a 1:1 mixture of N,N-dimethylformamide and dichloromethane (0.02 – 0.2 mol/l) is admixed dropwise at 0°C with a 0.2 - 1.0 molar solution of diisopropylethylamine (2.5 to 3.5 eq.) in N,N-dimethylformamide or a 1:1 mixture of N,N-dimethylformamide and dichloromethane over a period of 1 h. When the addition is over the reaction mixture is stirred at 0°C for another 30 minutes and at room temperature overnight, and then is concentrated under reduced pressure. The product can be obtained by chromatography on silica gel (mobile phases: mixtures of cyclohexane/ethyl acetate or mixtures of dichloromethane and ethanol) or by RP-HPLC (mobile phases: variable gradients of water and acetonitrile), or alternatively by a combination of both methods.

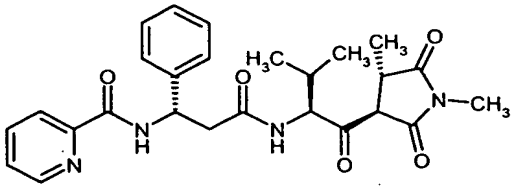
Alternatively the reaction may also take place in accordance with the following method:

A mixture of amine hydrochloride (1.0 eq.), carboxylic acid (1.2 to 1.3 eq.), triethylamine (2.4 – 3 eq.) and HOBt (2.4 – 3 eq.) in absolute dichloromethane or in a mixture of N,N-dimethylformamide and dichloromethane (0.02 – 0.2 mol/l) is admixed finally with 1.2 eq. of EDC. The reaction mixture is stirred at room temperature (2 h to overnight) before being concentrated under reduced pressure. The residue is taken up in ethyl acetate or dichloromethane and the organic phase is washed with water, saturated sodium hydrogencarbonate solution and saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. The product can be purified by chromatography on silica gel (mobile phases: mixtures of cyclohexane/ethyl acetate or mixtures of dichloromethane and ethanol) or by RP-HPLC (mobile phases: variable gradients of water and acetonitrile), or alternatively by a combination of both methods.

In accordance with the above-described instructions for the acylation of 3-[2-aminoalkanoyl]-2,5-pyrrolidinedione hydrochloride derivatives or of acylalkylamino substituted 3-[2-aminoalkanoyl]-2,5-pyrrolidinedione hydrochloride derivatives with carboxylic acid derivatives it is possible to obtain the following compounds.

Example 1

N-{(1*S*)-3-[((1*S*)-1-{[(3*R*,4*S*)-1,4-Dimethyl-2,5-dioxo-3-pyrrolidinyl]carbonyl}-2-methylpropyl)amino]-3-oxo-1-phenylpropyl}-2-pyridinecarboxamide



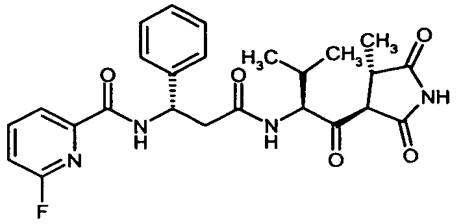
^{1}H-NMR (200 MHz, d_6-DMSO): δ = 9.59 (d, 1 H), 8.65 (d, 1 H), 8.21 (d, 1 H), 7.98 (d, 2 H), 7.61 (q, 1 H), 7.42-7.16 (m, 5 H), 5.48-5.32 (m, 1 H), 4.76 (dd, 1 H), 3.99 (d, 1 H), 3.20-2.92 (m, 2 H), 2.82 (s, 3 H), 2.61 (dd, 1 H), 2.32-2.13 (m, 1 H), 1.13 (d, 3 H), 0.65 (d, 3 H), 0.59 (d, 3 H).

MS (ES+): m/z (%) = 479 $(M+H)^+$ (80).

HPLC (method 5): R_t = 3.79 min.

Example 2

6-Fluoro-N-{(1*S*)-3-[((1*S*)-2-methyl-1-{[(3*R*,4*S*)-4-methyl-2,5-dioxo-3-pyrrolidinyl]-carbonyl}propyl)amino]-3-oxo-1-phenylpropyl}-2-pyridinecarboxamide



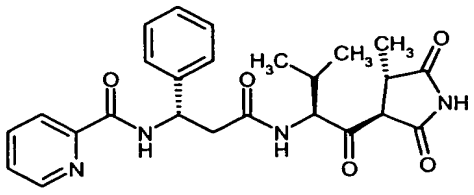
^{1}H-NMR (300 MHz, d_6-DMSO): δ = 11.31 (s, 1 H), 9.32 (d, 1 H), 8.22-8.10 (m, 2 H), 7.95-7.90 (m, 1 H), 7.45-7.18 (m, 6 H), 5.43-5.33 (m, 1 H), 4.70 (dd, 1 H), 4.02 (d, 1 H), 3.15 (dd, 1 H), 3.01-2.90 (m, 1 H), 2.62 (dd, 1 H), 2.30-2.18 (m, 1 H), 1.10 (d, 3 H), 0.62 (d, 3 H), 0.59 (d, 3 H).

MS (ES-): m/z (%) = 481 $(M-H)^-$ (100).

HPLC (method 3): R_t = 4.19 min.

Example 3

N-{(1*S*)-3-[((1*S*)-2-Methyl-1-{[(3R,4S)-4-methyl-2,5-dioxo-3-pyrrolidinyl]-carbonyl}propyl)amino]-3-oxo-1-phenylpropyl}-2-pyridinecarboxamide



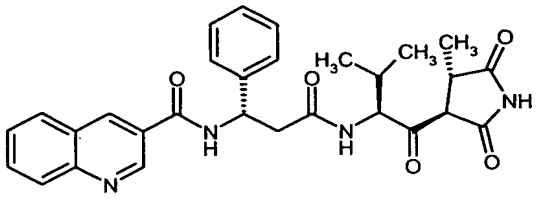
^{1}H-NMR (300 MHz, d_6-DMSO): δ = 11.32 (s, 1 H), 9.53 (d, 1 H), 8.69-8.65 (m, 1 H), 8.15 (d, 1 H), 8.02-7.98 (m, 2 H), 7.63-7.57 (m, 1 H), 7.40-7.18 (m, 5 H), 5.45-5.35 (m, 1 H), 4.67 (dd, 1 H), 4.00 (d, 1 H), 3.12 (dd, 1 H), 2.97 (dd, 1 H), 2.64 (dd, 1 H), 2.29-2.15 (m, 1 H), 1.10 (d, 3 H), 0.60 (d, 3 H), 0.56 (d, 3 H).

MS (ES+): m/z (%) = 465 $(M+H)^+$ (100).

HPLC (method 6): R_t = 3.65 min.

Example 4

N-{(1*S*)-3-[((1*S*)-2-Methyl-1-{[(3*R*,4*S*)-4-methyl-2,5-dioxo-3-pyrrolidinyl]-carbonyl}propyl)amino]-3-oxo-1-phenylpropyl}-3-quinolinecarboxamide



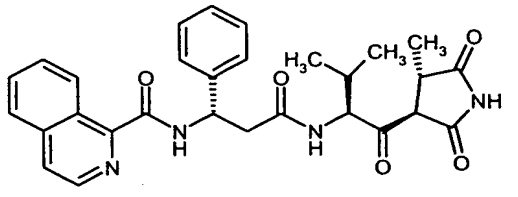
^{1}H-NMR (principal conformer) (300 MHz, d_6-DMSO): δ = 11.31 (s, 1 H), 9.29-9.12 (m, 2 H), 8.82-8.78 (m, 1 H), 8.15-8.07 (m, 3 H), 7.90-7.82 (m, 1 H), 7.72-7.68 (m, 1 H), 7.50-7.20 (m, 5 H), 5.59-5.48 (m, 1 H), 4.71 (dd, 1 H), 3.98 (d, 1 H), 3.04-2.70 (m, 3 H), 2.31-2.22 (m, 1 H), 1.09 (d, 3 H), 0.79 (d, 3 H), 0.68 (d, 3 H).

MS (ES+): m/z (%) = 515 $(M+H)^+$ (100).

HPLC (method 6): R_t = 3.52 min.

Example 5

N-{(1*S*)-3-[((1*S*)-2-Methyl-1-{[(3*R*,4*S*)-4-methyl-2,5-dioxo-3-pyrrolidinyl]-carbonyl}propyl)amino]-3-oxo-1-phenylpropyl}-1-isoquinolinecarboxamide



^{1}H-NMR (principal conformer) (400 MHz, d_6-DMSO): δ = 11.34 (s, 1 H), 9.56 (d, 1 H), 9.00 (d, 1 H), 8.58 (d, 1 H), 8.13 (d, 1 H), 8.04 (d, 2 H), 7.80 (t, 1 H), 7.70 (t, 1 H), 7.45 (d, 2 H), 7.34 (t, 2 H), 7.23 (t, 1 H), 5.52-5.45 (m, 1 H), 4.69 (dd, 1 H), 4.00

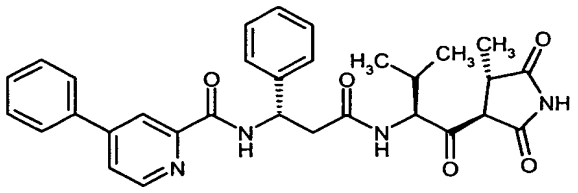
(d, 1 H), 3.10 (dd, 1 H), 2.97-2.88 (m, 1 H), 2.70-2.62 (m, 1 H), 2.21-2.12 (m, 1 H), 1.10 (d, 3 H), 0.59 (d, 3 H), 0.50 (d, 3 H).

MS (ES+): m/z (%) = 515 $(M+H)^+$ (100).

HPLC (method 6): R_t = 4.32 min.

Example 6

N-{(1*S*)-3-[((1*S*)-2-Methyl-1-{[(3*R*,4*S*)-4-methyl-2,5-dioxo-3-pyrrolidinyl]-carbonyl}propyl)amino]-3-oxo-1-phenylpropyl}-4-phenyl-2-pyridinecarboxamide



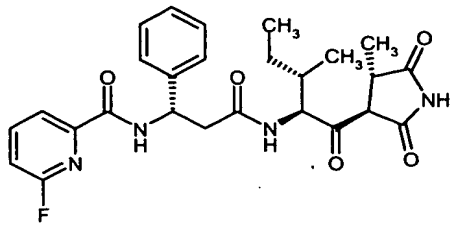
^{1}H-NMR (200 MHz, d_6-DMSO): δ = 11.36 (s, 1 H), 9.67 (d, 1 H), 8.72 (d, 1 H), 8.26-8.18 (m, 2 H), 7.98-7.92 (m, 1 H), 7.88-7.81 (m, 2 H), 7.60-7.50 (m, 3 H), 7.45-7.20 (m, 5 H), 5.50-5.38 (m, 1 H), 4.75-4.68 (m, 1 H), 4.02 (d, 1 H), 3.20-2.82 (m, 3 H), 2.25-2.15 (m, 1 H), 1.10 (d, 3 H), 0.61 (d, 3 H), 0.57 (d, 3 H).

MS (ES+): m/z (%) = 541 $(M+H)^+$ (100).

HPLC (method 14): R_t = 4.88 min.

Example 7

6-Fluoro-N-{(1*S*)-3-[((1*S*,2*S*)-2-methyl-1-{[(3*R*,4*S*)-4-methyl-2,5-dioxo-3-pyrrolidinyl]carbonyl}butyl)amino]-3-oxo-1-phenylpropyl}-2-pyridinecarboxamide



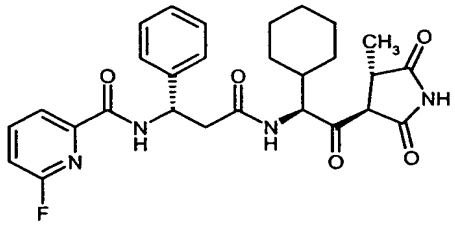
^{1}H-NMR (300 MHz, d_6-DMSO): δ = 11.33 (s, 1 H), 9.30 (d, 1 H), 8.22-8.12 (m, 2 H), 7.95-7.91 (m, 1 H), 7.45-7.20 (m, 6 H), 5.45-5.35 (m, 1 H), 4.67 (dd, 1 H), 4.03 (d, 1 H), 3.17-3.09 (m, 1 H), 2.97-2.88 (m, 1 H), 2.62-2.54 (m, 1 H), 2.02-1.90 (m, 1 H), 1.30-1.15 (m, 2 H), 1.12 (d, 3 H), 0.60 (d, 3 H), 0.56 (t, 3 H).

MS (ES+): m/z (%) = 497 $(M+H)^+$ (100).

HPLC (method 12): R_t = 2.95 min.

Example 8

N-[(1*S*)-3-({(1*S*)-1-Cyclohexyl-2-[(3*R*,4*S*)-4-methyl-2,5-dioxo-3-pyrrolidinyl]-2-oxoethyl}amino)-3-oxo-1-phenylpropyl]-6-fluoro-2-pyridinecarboxamide



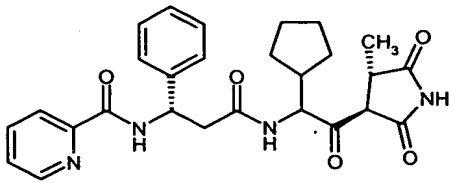
^{1}H-NMR (principal conformer) (200 MHz, d_6-DMSO): δ = 11.35 (s, 1 H), 9.40 (d, 1 H), 8.27-8.10 (m, 2 H), 7.99-7.90 (m, 1 H), 7.50-7.18 (m, 6 H), 5.46-5.32 (m, 1 H), 4.73 (dd, 1 H), 4.08 (d, 1 H), 3.26-3.10 (m, 1 H), 3.00-2.80 (m, 2 H), 1.98-1.80 (m, 1 H), 1.60-1.25 (m, 5 H), 1.12 (d, 3 H), 1.10-0.65 (m, 5 H).

MS (ES+): m/z (%) = 523 $(M+H)^+$ (100).

HPLC (method 12): R_t = 3.12 min.

Example 9

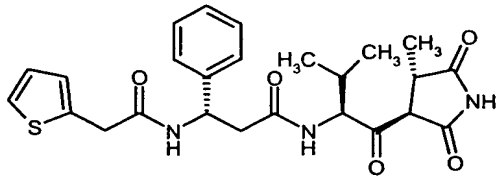
N-[(1*S*)-3-({1-Cyclopentyl-2-[(3*R*,4*S*)-4-methyl-2,5-dioxo-3-pyrrolidinyl]-2-oxoethyl}amino)-3-oxo-1-phenylpropyl]-2-pyridinecarboxamide



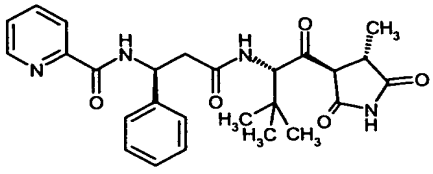
^{1}H-NMR (2 diastereomers, approximately 2:1 ratio; a number of conformers) (400 MHz, d_6-DMSO): δ = 11.35 + 11.31 (2x s, 1 H), 9.56 + 9.51-9.41 (d + m, 1 H), 8.71-8.63 (m, 1 H), 8.60-8.42 + 8.30 (m + d, 1 H), 8.02-7.92 (m, 2 H), 7.65-7.57 (m, 1 H), 7.42-7.18 (m, 5 H), 5.48-5.37 (m, 1 H), 4.65 + 4.45-4.28 (t + m, 1 H), 3.99 + 3.87 + 3.80 (d + t + d, 1 H), 3.13 + 3.07-2.98 (dd + m, 1 H), 2.95-2.80 (m, 1 H), 2.70-2.58 (m, 1 H), 2.36-2.18 (m, 1 H), 1.65-0.85 (m, 8 H), 1.12 + 1.01 (2x d, 3 H).
MS (ES+): m/z (%) = 491 $(M+H)^+$ (100).
HPLC (method 12): R_t = 2.79 min.

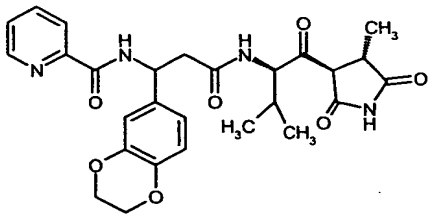
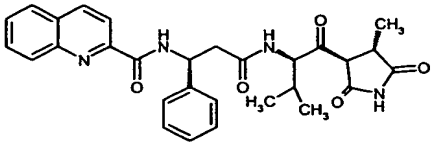
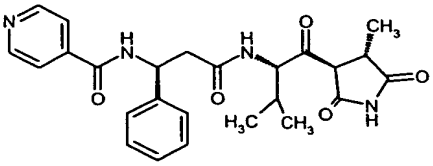
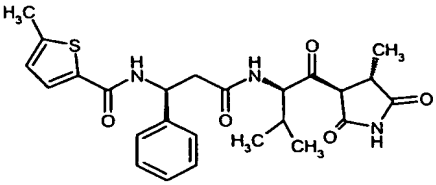
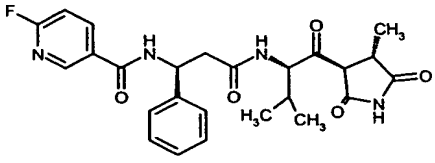
Example 10

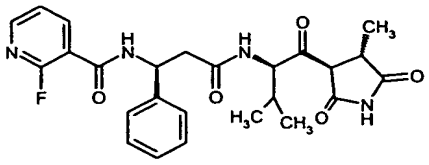
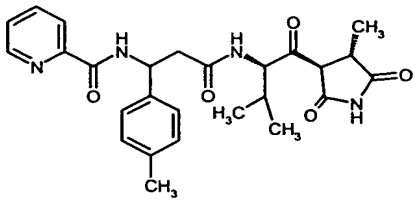
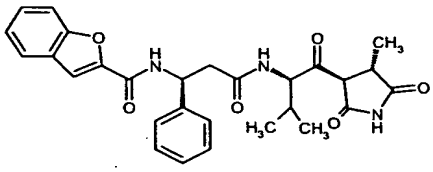
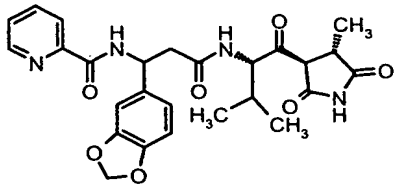
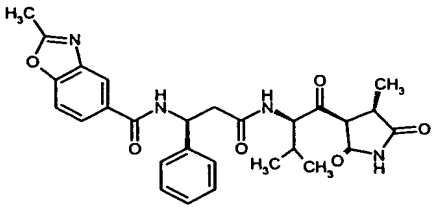
(3*S*)-N-((1*S*)-2-Methyl-1-{[(3*R*,4*S*)-4-methyl-2,5-dioxo-3-pyrrolidinyl]carbonyl}-propyl)-3-phenyl-3-[(2-thienylacetyl)amino]propanamide

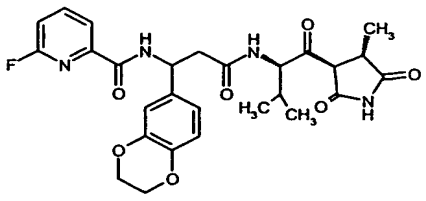
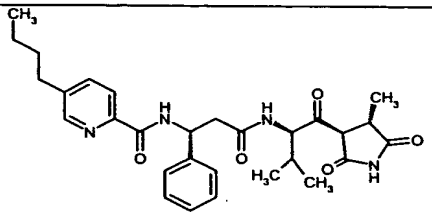
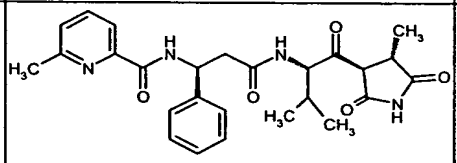
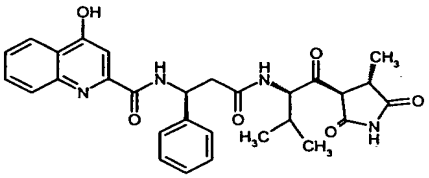
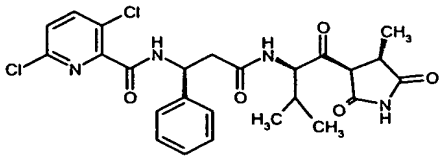
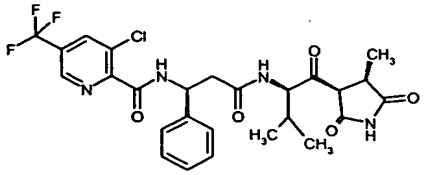


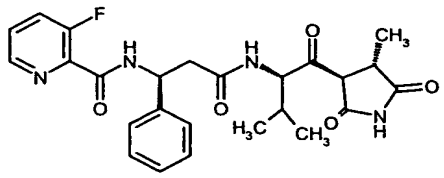
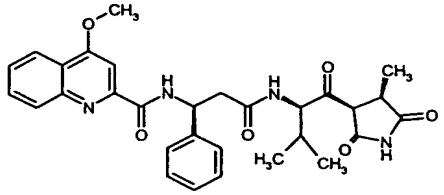
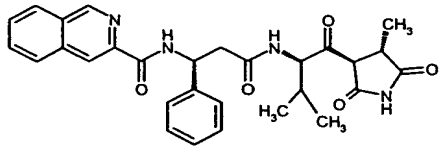
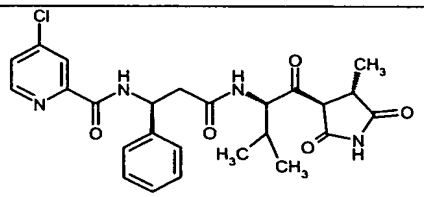
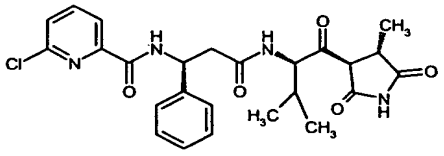
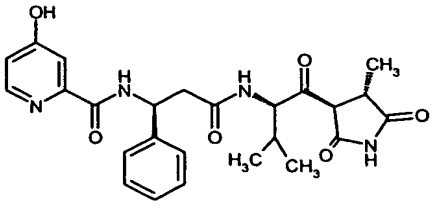
^{1}H-NMR (300 MHz, d_6-DMSO): δ = 11.31 (s, 1 H), 8.50 (d, 1 H), 8.08 (d, 1 H), 7.34-7.18 (m, 6 H), 6.95-6.90 (m, 1 H), 6.89-6.85 (m, 1 H), 5.25-5.16 (m, 1 H), 4.61 (dd, 1 H), 3.91 (d, 1 H), 3.66 (d, 2 H), 2.90 (dd, 1 H), 2.80-2.60 (m, 2 H), 2.32-2.23 (m, 1 H), 1.07 (d, 3 H), 0.81 (d, 3 H), 0.75 (d, 3 H).
MS (ES-): m/z (%) = 482 $(M-H)^-$ (100).
HPLC (method 5): R_t = 3.72 min.

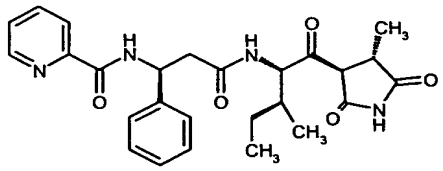
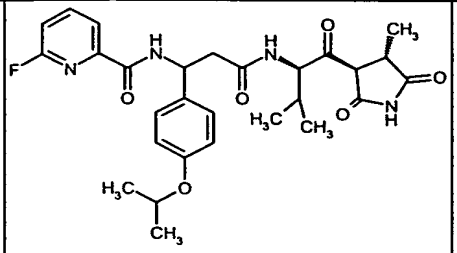
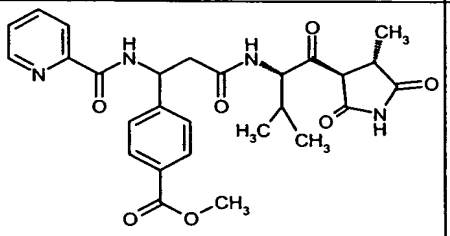
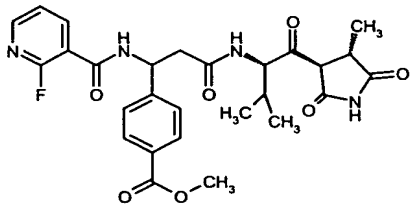
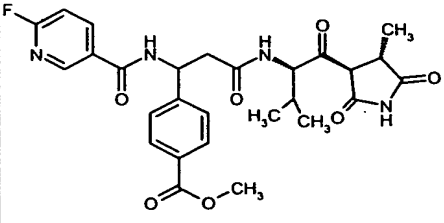
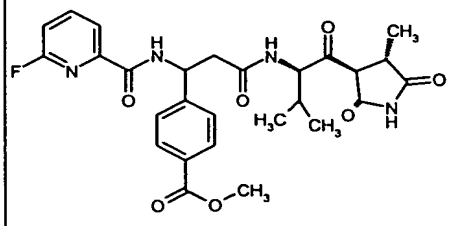
Example	Structure	MW	MS	HPLC
11		478.55	MS (ES+), m/z (%): 479 $(M+H)^+$ (100)	HPLC (method 5) R_t = 3.69 min

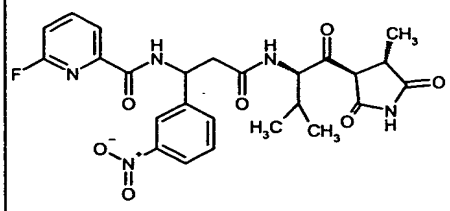
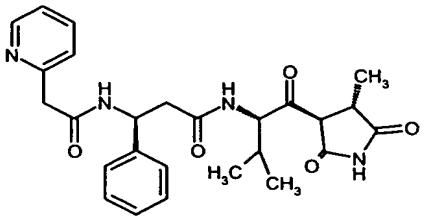
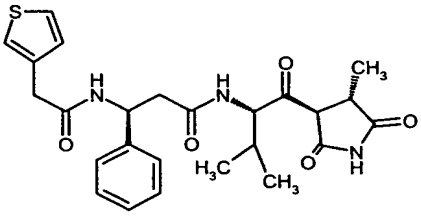
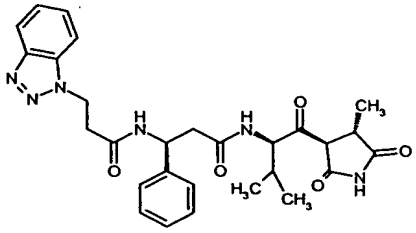
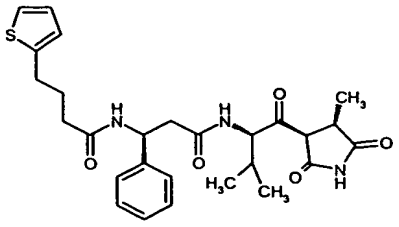
Example	Structure	MW	MS	HPLC
12		522.55	MS (ES+), m/z (%): 523 $(M+H)^+$ (75)	HPLC (method 9) R_t = 3.81 min
13		514.58	MS (ES+), m/z (%): 515 $(M+H)^+$ (100)	HPLC (method 5) R_t = 3.97 min
14		464.52	MS (ES+), m/z (%): 465 $(M+H)^+$ (100)	HPLC (method 5) R_t = 3.01 min
15		483.59	MS (ES+), m/z (%): 506 $(M+Na)^+$ (100)	HPLC (method 5) R_t = 3.74 min
16		482.51	MS (ES+), m/z (%): 505 $(M+Na)^+$ (100)	HPLC (method 6) R_t = 3.48 min

Example	Structure	MW	MS	HPLC
17		482.51	MS (ES-), m/z (%): 481 ($M-H^+$) (100)	HPLC (method 6) R_t = 3.46 min
18		478.55	MS (ES+), m/z (%): 479 $(M+H)^+$ (45)	HPLC (method 9) R_t = 4.03 min
19		503.55	MS (ES+), m/z (%): 523 $(M+Na)^+$ (100)	HPLC (method 6) R_t = 3.94 min
20		508.53	MS (ES+), m/z (%): 509 ($M+H^+$) (90)	HPLC (method 9) R_t = 3.82 min
21		518.57	MS (ES+), m/z (%): 519 $(M+H)^+$ (100)	HPLC (method 3) R_t = 3.95 min

Example	Structure	MW	MS	HPLC
22		540.55	MS (ES+), m/z (%): 541 $(M+H)^+$ (35)	HPLC (method 9) R_t = 3.92 min
23		520.63	MS (ES-), m/z (%): 519 $(M-H)^-$ (100)	HPLC (method 5) R_t = 4.6 min
24		478.55	MS (ES-), m/z (%): 477 $(M-H)^-$ (100)	HPLC (method 5) R_t = 3.9 min
25		530.58	MS (ES+), m/z (%): 531 $(M+H)^+$ (100)	HPLC (method 6) R_t = 3.70 min
26		533.41	MS (ES+), m/z (%): 533 $(M+H^+)$ (100)	HPLC (method 6) R_t = 4.20 min
27		566.96	MS (ES+), m/z (%): 567 $(M+H^+)$ (100)	HPLC (method 6) R_t = 4.42 min

Example	Structure	MW	MS	HPLC
28		482.51	MS (ES+), m/z (%): 483 $(M+H)^+$ (100)	HPLC (method 11) R_t = 2.66 min
29		544.60	MS (ES+), m/z (%): 545 $(M+H)^+$ (100)	HPLC (method 14) R_t = 4.5 min
30		514.58	MS (ES-), m/z (%): 513 $(M-H)^-$ (100)	HPLC (method 14) R_t = 4.40 min
31		498.96	MS (ES-), m/z (%): 497 $(M-H)^-$ (100)	HPLC (method 14) R_t = 4.37 min
32		498.96	MS (ES+), m/z (%): 521 $(M+Na)^+$ (100)	HPLC (method 13) R_t = 4.05 min
33		480.52	MS (ES+), m/z (%): 481 $(M+H)^+$ (100)	HPLC (method 14) R_t = 3.65 min

Example	Structure	MW	MS	HPLC
34		478.55	MS (ES+), m/z (%): 479 $(M+H)^+$ (100)	HPLC (method 13) R_t = 3.98 min
35		540.59	MS (ES-), m/z (%): 539 $(M-H)^-$ (100)	HPLC (method 11) R_t = 2.73 min
36		522.55	MS (ES-), m/z (%): 521 $(M-H)^-$ (100)	HPLC (method 5) R_t = 3.67 min
37		540.55	MS (ES+), m/z (%): 541 $(M+H)^+$ (100)	HPLC (method 9) R_t = 3.75 min
38		540.55	MS (ES+), m/z (%): 541 $(M+H)^+$ (100)	HPLC (method 9) R_t = 3.80 min
39		540.55	MS (ES+), m/z (%): 541 $(M+H)^+$ (100)	HPLC (method 14) R_t = 4.12 min

Example	Structure	MW	MS	HPLC
40		527.51	MS (ES+), m/z (%): 528 $(M+H)^+$ (100)	HPLC (method 12) R_t = 2.76 min
41		478.55	MS (ES+), m/z (%): 479 $(M+H)^+$ (100)	HPLC (method 5) R_t = 2.64 min
42		483.59	MS (ES+), m/z (%): 484 $(M+H)^+$ (100)	HPLC (method 15) R_t = 2.94 min
43		532.60	MS (ES+), m/z (%): 555 $(M+Na)^+$ (100)	HPLC (method 5) R_t = 3.52 min
44		511.64	MS (ES+), m/z (%): 534 $(M+Na)^+$ (100)	HPLC (method 5) R_t = 4.00 min

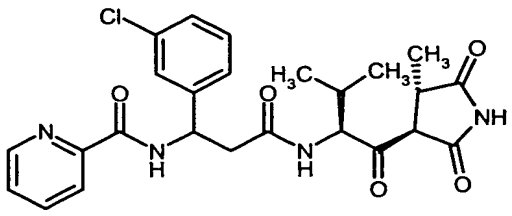
General instructions I: Solid-phase-supported synthesis

The aldehyde resin (Nova Biochem) (0.78 mmol/g) is suspended in toluene/trimethyl orthoformate (1:1 to 4:1), admixed with the corresponding beta-amino acid methyl

ester (2.5 - 3 eq) at room temperature and shaken overnight. The resin is washed twice with N,N-dimethylformamide, suspended in N,N-dimethylformamide and admixed with tetrabutylammonium borohydride (2 – 5 eq) at room temperature. After 30 minutes of shaking at room temperature the reaction mixture is slowly admixed with glacial acetic acid (100 eq) at from –40°C to room temperature, optionally warmed to room temperature again and shaken for at least 1 h. The resin is washed repeatedly with water, methanol, dichloromethane/10% N,N-diisopropylethylamine, methanol, dichloromethane and diethyl ether and dried. The resin is suspended in dichloromethane and shaken with N,N-diisopropylethylamine (10 - 20 eq) and with the corresponding carbonyl chloride (5 eq) at room temperature for 1 - 2 h. The resin is washed repeatedly with methanol, N,N-dimethylformamide, methanol, dichloromethane and diethyl ether and dried. For hydrolysis the resin is admixed with a solution of potassium hydroxide (30 eq) in methanol/dioxane (1:2, 30 mg potassium hydroxide/ml solution) and shaken at RT for 3 h. Subsequently the resin is washed with water, methanol, dichloromethane/glacial acetic acid, dichloromethane, dichloromethane/N,N-diisopropylethylamine, methanol, N,N-dimethylformamide, methanol, dichloromethane and diethyl ether. The resin is shaken with (benzotriazol-1-yloxy)bisdimethylaminomethylium fluoroborate (5 eq) and N,N-diisopropyl-ethylamine (20 eq) in N,N-dimethylacetamide at RT for 1 h, washed twice with N,N-dimethylacetamide, admixed with a freshly prepared solution of (3*R*,4*S*)-3-[(2*S*)-2-amino-3-methylbutanoyl]-4-methyl-2,5-pyrrolidinedione hydrochloride (1.5 - 2 eq) and N,N-diisopropylethylamine (20 eq) and shaken at RT for 3 h. Finally the resin is washed repeatedly with methanol, N,N-dimethylformamide, water, N,N-dimethylformamide, methanol, dichloromethane and diethyl ether and dried. The resin is shaken with trifluoroacetic acid or 50% strength trifluoroacetic acid in dichloromethane at from RT to 50°C for from 30 minutes to 3 h. The crude product solution is filtered, evaporated to dryness and purifed by reversed phase HPLC using a water/acetonitrile gradient. An alternative possibility is chromatography on silica gel (mobile phases: mixtures of dichloromethane and methanol).

Example 45

N-{1-(3-Chlorophenyl)-3-[((1S)-2-methyl-1-{[(3R,4S)-4-methyl-2,5-dioxo-3-pyrrolidinyl]carbonyl}propyl)amino]-3-oxopropyl}-2-pyridinecarboxamide



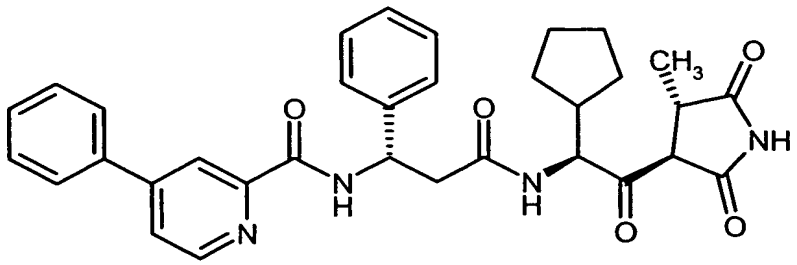
^{1}H-NMR (2 diastereoisomers, ratio 1:1, 300 MHz, DMSO-d_6): δ = 11.3 (d, 1H), 9.64 (d, 0.5 H), 9.45 (d, 0.5 H), 8.70-8.62 (m, 1 H), 8.28 (d, 0.5 H), 8.18 (d, 0.5 H), 8.02-7.94 (m, 2 H), 7.65-7.56 (m, 1 H), 7.50-7.41 (m, 1 H), 7.38-7.21 (m, 3 H), 5.48-5.32 (m, 1 H), 4.69 (dd, 0.5 H), 4.60 (dd, 0.5 H), 4.02 (d, 0.5 H), 3.93 (d, 0.5 H), 3.10-2.60 (m, 3 H), 2.35-2.15 (m, 1 H), 1.15-1.03 (m, 3 H), 0.75-0.54 (m, 6 H).

MS (ES+): m/z (%) = 499 $(M+H)^+$ (100).

HPLC (method 6): R_t = 3.95 min.

Example 46

N-[(1*S*)-3-({(1*S*)-1-Cyclopentyl-2-[(3*R*,4*S*)-4-methyl-2,5-dioxo-3-pyrrolidinyl]-2-oxoethyl}amino)-3-oxo-1-phenylpropyl]-4-phenyl-2-pyridinecarboxamide



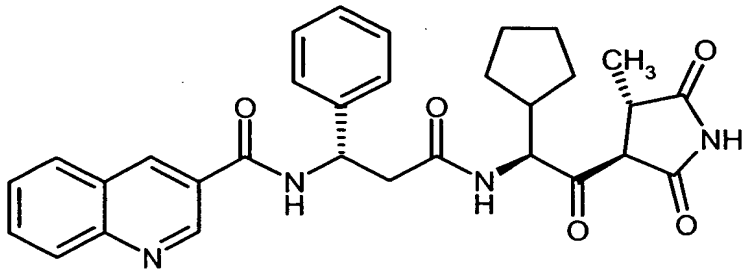
^{1}H-NMR (300 MHz, d_6-DMSO): δ = 11.33 (s, 1 H), 9.59 (d, 1 H), 8.74 (d, 1 H), 8.31 (d, 1 H), 8.23 (s, 1H), 7.98-7.89 (m, 1 H), 7.87-7.77 (m, 2H), 7.59-7.19 (m, 8 H), 5.50-5.38 (m, 1 H), 4.62 (t, 1 H), 3.99 (d, 1 H), 3.48-3.00 (m, 2 H), 2.96-2.83 (m, 1 H), 2.75-2.18 (m, 4 H), 1.53-0.71 (m, 5 H), 1.08 (d, 3 H).

MS (ES+): m/z = 567 ($M+H^+$).

HPLC (method 19): R_t = 4.28 min.

Example 47

N-[(1*S*)-3-({(1*S*)-1-Cyclopentyl-2-[(3*R*,4*S*)-4-methyl-2,5-dioxo-3-pyrrolidinyl]-2-oxoethyl}amino)-3-oxo-1-phenylpropyl]-3-quinolinecarboxamide



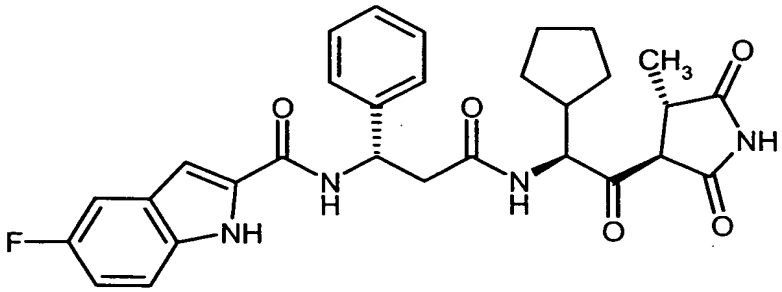
^{1}H-NMR (300 MHz, d_6-DMSO): δ = 11.34 (s, 1 H), 9.32 (d, 1 H), 9.22 (d, 1 H), 8.93 (d, 1 H), 8.32 (d, 1H), 8.11 (d, 2H), 7.89 (dt, 1H), 7.72 (t, 1H), 7.50-7.19 (m, 5 H), 5.58-5.44 (m, 1 H), 4.61 (t, 1 H), 3.93 (d, 1H), 3.77-3.55 (m, 1H), 3.10-2.21 (m, 5 H), 1.60-0.96 (m, 6 H), 1.09 (d, 3 H).

MS (ESI+): m/z = 541 ($M+H^+$).

HPLC (method 19): R_t = 4.04 min.

Example 48

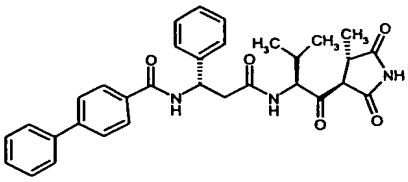
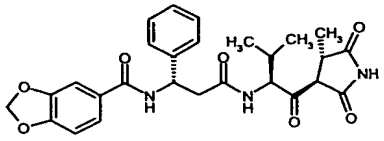
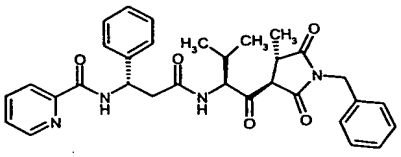
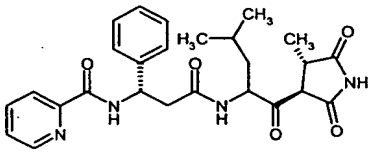
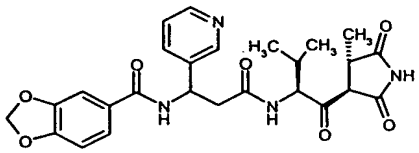
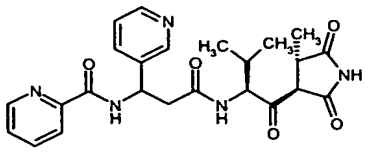
N-[(1*S*)-3-({(1*S*)-1-Cyclopentyl-2-[(3*R*,4*S*)-4-methyl-2,5-dioxo-3-pyrrolidinyl]-2-oxoethyl}amino)-3-oxo-1-phenylpropyl]-5-fluoro-1H-indole-2-carboxamide

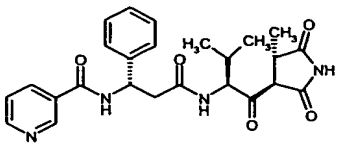
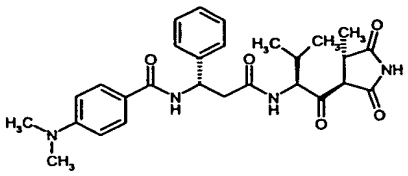
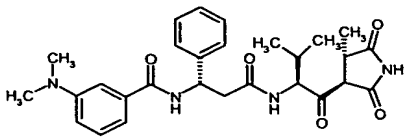
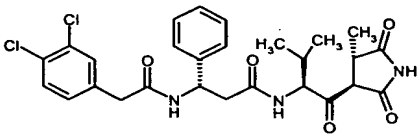
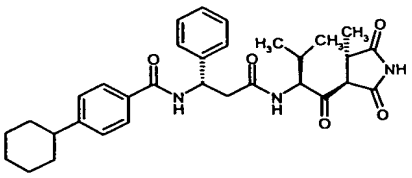
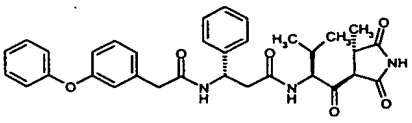
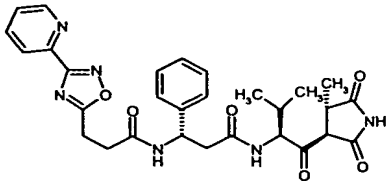


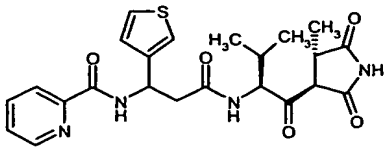
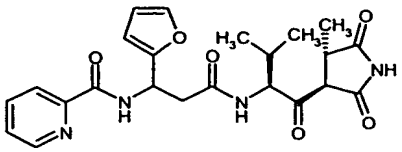
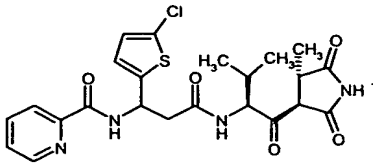
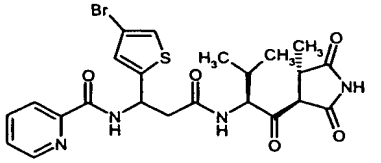
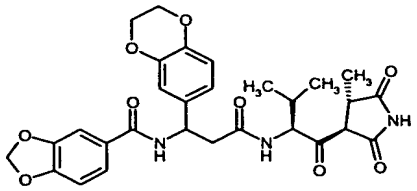
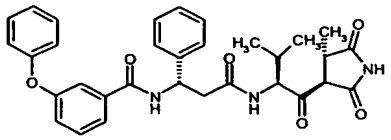
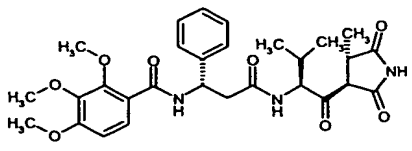
^{1}H-NMR (200 MHz, d_6-DMSO): δ = 11.66 (s, 1 H), 11.37 (s, 1H), 8.83 (d, 1H), 8.27 (d, 1H), 7.48-6.94 (m, 9 H) 5.54-5.36 (m, 1 H), 4.71-4.61 (m, 1H), 3.98 (d, 1 H), 3.28-3.19 (m, 1 H), 3.01-2.11 (m, 6 H), 1.54-0.97 (m, 5 H), 1.08 (d, 3 H).

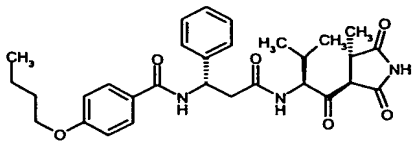
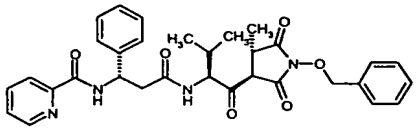
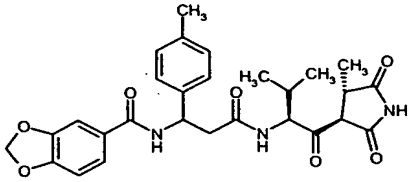
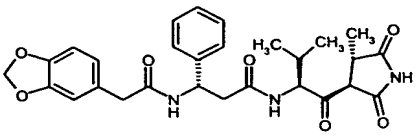
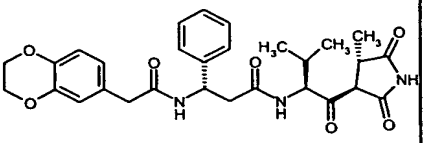
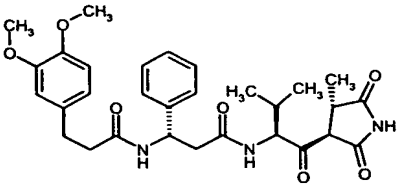
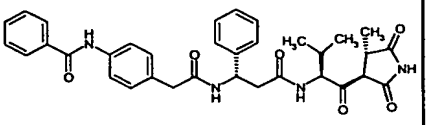
MS (ESI+): m/z = 547 ($M+H^+$).

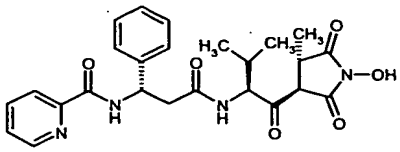
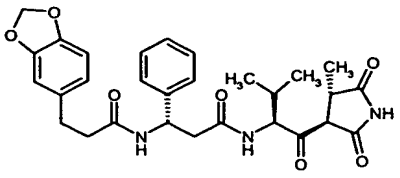
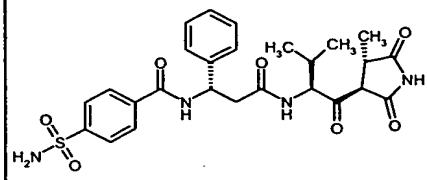
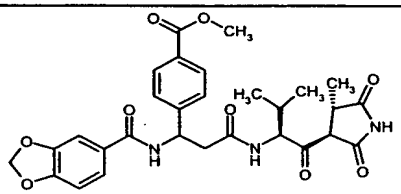
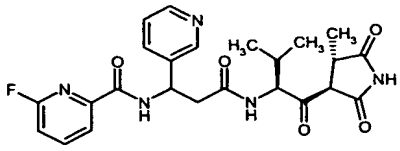
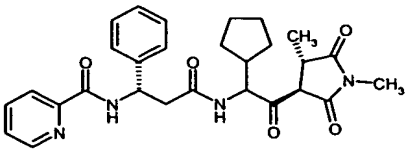
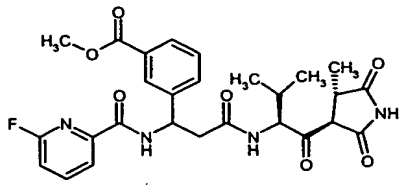
HPLC (method 19): R_t = 3.44 min.

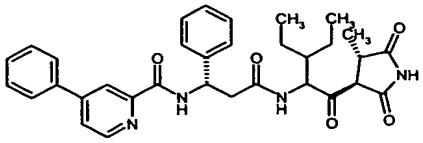
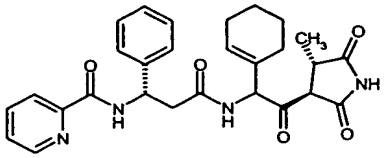
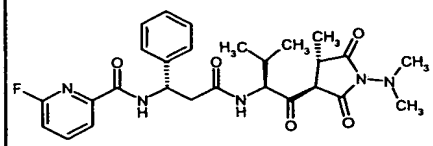
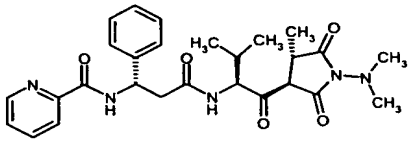
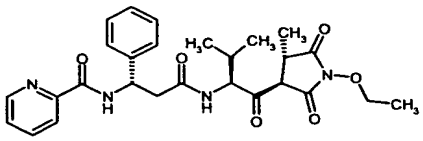
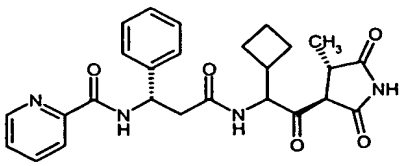
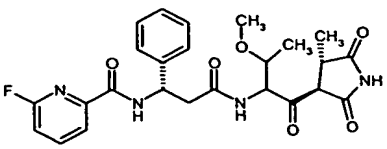
Example	Structure	MW	MS	HPLC
49		539.63	MS (ES+), m/z: 540 $(M+H)^+$	HPLC (method 5): R_t = 4.22 min
50		507.54	MS (ES+), m/z: 508 $(M+H)^+$	HPLC (method 5): R_t = 3.61 min
51		554.64	MS (ES+), m/z: 555 $(M+H)^+$	HPLC (method 8): R_t = 2.72 min
52		478.55	MS (ES+), m/z: 479 $(M+H)^+$	HPLC (method 5): R_t = 3.67 min
53		508.53	MS (ES+), m/z: 509 $(M+H)^+$	HPLC (method 5): R_t = 2.45 and 2.52 min
54		465.51	MS (ES+), m/z: 466 $(M+H)^+$	

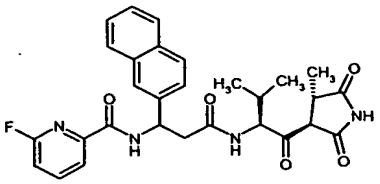
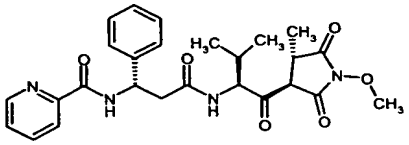
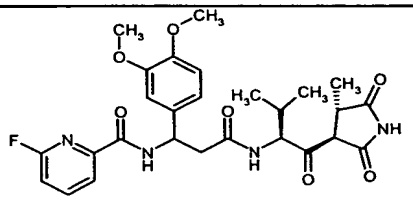
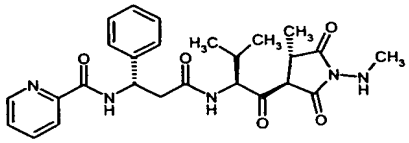
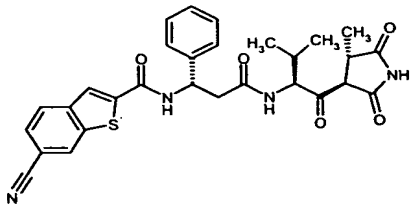
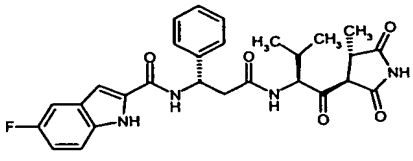
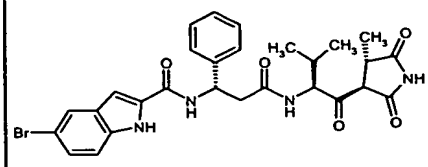
Ex-ample	Structure	MW	MS	HPLC
55		464.52	MS (ES+), m/z: 465 $(M+H)^+$	HPLC (method 5): R_t = 3.02 min
56		506.60	MS (ES+), m/z: 507 $(M+H)^+$	HPLC (method 5): R_t = 3.72 min
57		506.60	MS (ES+), m/z: 507 $(M+H)^+$	HPLC (method 5): R_t = 3.62 min
58		546.45	MS (ES+), m/z: 546 $(M+H)^+$	HPLC (method 8): R_t = 2.60 min
59		545.68	MS (ES+), m/z: 546 $(M+H)^+$	HPLC (method 5): R_t = 4.65 min
60		569.65	MS (ES+), m/z: 570 $(M+H)^+$	HPLC (method 5): R_t = 4.19 min
61		560.61	MS (ES+), m/z: 561 $(M+H)^+$	HPLC (method 5): R_t = 3.28 min

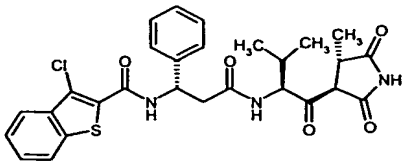
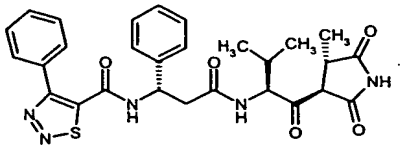
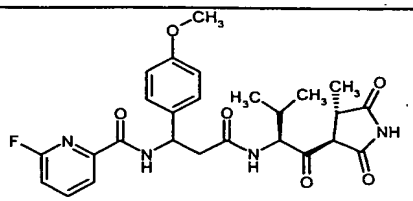
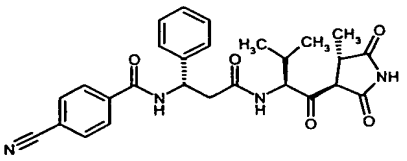
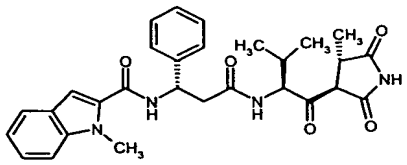
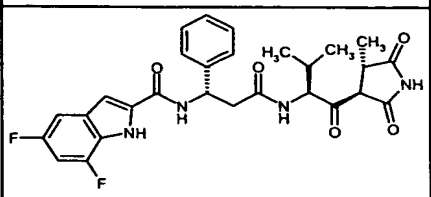
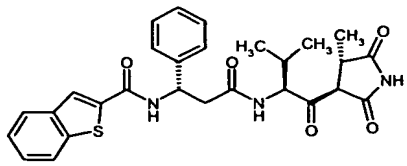
Example	Structure	MW	MS	HPLC
62		470.55	MS (ES+), m/z: 471 $(M+H)^+$	HPLC (method 5): R_t = 3.5 min
63		454.48	MS (ES+), m/z: 455 $(M+H)^+$	HPLC (method 5): R_t = 3.4 min
64		504.99	MS (ES+), m/z: 505 $(M+H)^+$	HPLC (method 5): R_t = 3.8 min
65		549.44	MS (ES+), m/z: 551 $(M+H)^+$	HPLC (method 5): R_t = 3.8 min
66		565.58	MS (ES+), m/z: 566 $(M+H)^+$	HPLC (method 5): R_t = 3.5 min
67		555.63	MS (ES-), m/z: 554 $(M-H)^-$	HPLC (method 6): R_t = 4.28 min
68		553.61	MS (ES+), m/z: 554 $(M+H)^+$	HPLC (method 6): R_t = 3.85 min

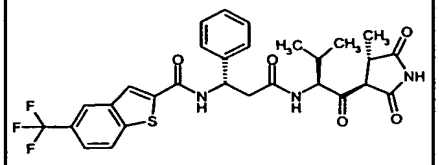
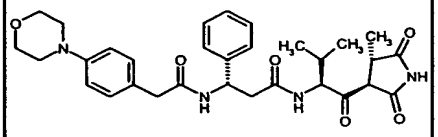
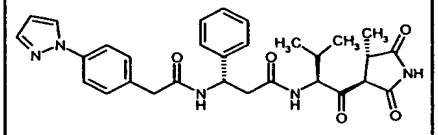
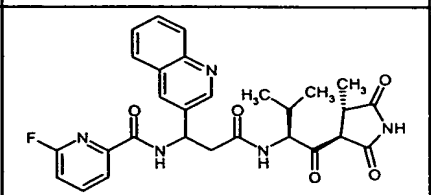
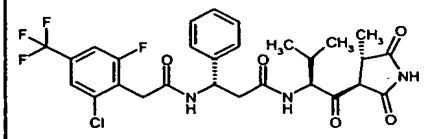
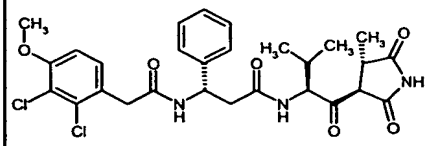
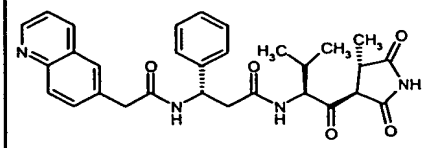
Example	Structure	MW	MS	HPLC
69		535.64	MS (ES+), m/z: 536 $(M+H)^+$	HPLC (method 6): R_t = 4.34 min
70		570.64	MS (ES+), m/z: 571 $(M+H)^+$	HPLC (method 5): R_t = 4.48 min
71		521.57	MS (ES+), m/z: 522 $(M+H)^+$	HPLC (method 9): R_t = 4.05 min
72		521.57	MS (ES+), m/z: 522 $(M+H)^+$	HPLC (method 5): R_t = 3.73 min
73		535.59	MS (ES-), m/z: 534 $(M-H)^-$	HPLC (method 5): R_t = 3.71 min
74		551.64	MS (ES-), m/z: 550 $(M-H)^-$	HPLC (method 5): R_t = 3.65 min
75		596.68	MS (ES+), m/z: 597 $(M+H)^+$	HPLC (method 6): R_t = 3.78 min

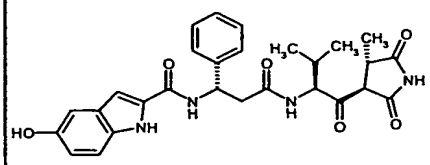
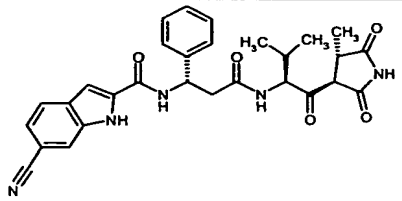
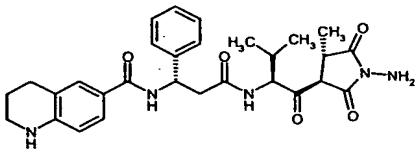
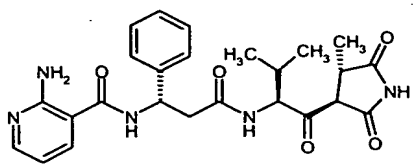
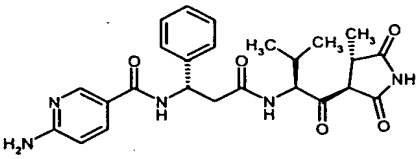
Example	Structure	MW	MS	HPLC
76		480.52	MS (ES+), m/z: 481 $(M+H)^+$	HPLC (method 5): R_t = 3.63 min
77		535.59	MS (ES+), m/z: 536 $(M+H)^+$	HPLC (method 6): R_t = 3.76 min
78		542.61	MS (ES-), m/z: 541 $(M-H)^-$	HPLC (method 5): R_t = 3.39 min
79		565.58	MS (ES+), m/z: 566 $(M+H)^+$	HPLC (method 14): R_t = 4.19 min
80		483.50	MS (ES+), m/z: 484 $(M+H)^+$	HPLC (method 9): R_t = 2.93 min
81		504.58	MS (ES+), m/z: 505 $(M+H)^+$	HPLC (method 17): R_t = 3.57 min
82		540.55	MS (ES+), m/z: 563 $(M+Na)^+$	HPLC (method 14): R_t = 4.25 min

Example	Structure	MW	MS	HPLC
83		568.67	MS (ES+), m/z: 570 $(M+H)^+$	HPLC (method 18): R_t = 3.96 min
84		502.57	MS (ES+), m/z: 503 $(M+H)^+$	HPLC (method 20): R_t = 3.45 min
85		525.58	MS (ES+), m/z: 526 $(M+H)^+$	HPLC (method 20): R_t = 3.55 min
86		507.59	MS (ES+), m/z: 508 $(M+H)^+$	HPLC (method 20): R_t = 3.43 min
87		508.57	MS (ES+), m/z: 509 $(M+H)^+$	HPLC (method 20): R_t = 3.60 min
88		476.53	MS (ES+), m/z: 477 $(M+H)^+$	HPLC (method 20): R_t = 3.12 min
89		498.51	MS (ES+), m/z: 499 $(M+H)^+$	HPLC (method 18): R_t = 3.35 min

Example	Structure	MW	MS	HPLC
90		532.57	MS (ES+), m/z: 533 $(M+H)^+$	HPLC (method 19): R_t = 4.24 min
91		494.55	MS (ES+), m/z: 495 $(M+H)^+$	HPLC (method 19): R_t = 3.47 min
92		542.56	MS (ES+), m/z: 543 $(M+H)^+$	HPLC (method 20): R_t = 3.02 min
93		493.56	MS (ES+), m/z: 494 $(M+H)^+$	HPLC (method 19): R_t = 4.06 min
94		544.63	MS (ES+), m/z: 545 $(M+H)^+$	HPLC (method 20): R_t = 3.42 min
95		520.56	MS (ES+), m/z: 521 $(M+H)^+$	HPLC (method 19): R_t = 4.17 min
96		581.46	MS (ES+), m/z: 583 $(M+H)^+$	HPLC (method 18): R_t = 3.6 min

Example	Structure	MW	MS	HPLC
97		554.06	MS (ES+), m/z: 554 $(M+H)^+$	HPLC (method 19): R_t = 4.17 min
98		547.63	MS (ES+), m/z: 548 $(M+H)^+$	HPLC (method 19): R_t = 4.01 min
99		512.54	MS (ES+), m/z: 513 $(M+H)^+$	HPLC (method 19): R_t = 4.04 min
100		488.54	MS (ES+), m/z: 489 $(M+H)^+$	HPLC (method 20): R_t = 3.15 min
101		516.60	MS (ES+), m/z: 517 $(M+H)^+$	HPLC (method 18): R_t = 3.5 min
102		538.55	MS (ES+), m/z: 539 $(M+H)^+$	HPLC (method 18): R_t = 3.5 min
103		519.62	MS (ES+), m/z: 520 $(M+H)^+$	HPLC (method 18): R_t = 3.5 min

Example	Structure	MW	MS	HPLC
104		587.62	MS (ES+), m/z: 588 $(M+H)^+$	HPLC (method 18): R_t = 3.7 min
105		562.66	MS (ES+), m/z: 563 $(M+H)^+$	HPLC (method 19): R_t = 2.42 min
106		543.62	MS (ES+), m/z: 544 $(M+H)^+$	HPLC (method 18): R_t = 3.2 min
107		533.56	MS (ES+), m/z: 534 $(M+H)^+$	HPLC (method 20): R_t = 2.45 min
108		597.99	MS (ES+), m/z: 598 $(M+H)^+$	HPLC (method 18): R_t = 3.6 min
109		576.47	MS (ES+), m/z: 576 $(M+H)^+$	HPLC (method 18): R_t = 3.5 min
110		528.61	MS (ES+), m/z: 529 $(M+H)^+$	HPLC (method 18): R_t = 2.6 min

Example	Structure	MW	MS	HPLC
111		518.57	MS (ES+), m/z: 519 $(M+H)^+$	HPLC (method 19): R_t = 2.26 min
112		527.58	MS (ES+), m/z: 528 $(M+H)^+$	HPLC (method 19): R_t = 2.61 min
113		533.63	MS (ES+), m/z: 534 $(M+H)^+$	HPLC (method 19): R_t = 2.55 min
114		479.53	MS (ES+), m/z: 480 $(M+H)^+$	HPLC (method 20): R_t = 1.97 min
115		479.53	MS (ES+), m/z: 480 $(M+H)^+$	HPLC (method 19): R_t = 1.82 min

B) **Evaluation of physiological activity**

The suitability of the compounds of the invention for treating bacterial diseases can be demonstrated in the following animal models:

Determination of the minimum inhibitory concentration (MIC):

The MIC is determined in a liquid dilution test. Overnight cultures of the test organisms are diluted to a cell count of 10^5 organisms per ml in Isosensitest medium (Difco, Irvine, USA) and are incubated with dilutions of the test substances (1:2 dilution stages). Exceptions are the tests with S. pneumoniae G9A, which are conducted in BHI broth (Difco) plus 20% bovine serum, and with H. influenzae, which are conducted in BHI broth (Difco) plus 20% bovine serum, 10 µg/ml hemin and 1% Isovitale (Becton Dickinson, New Jersey, USA).

The cultures are incubated at 37°C for 18-24 hours; S. pneumoniae and H. influenzae in the presence of 8 –10% CO_2.

Results:

The lowest concentration of each substance at which there is no longer any visible bacterial growth is defined as the MIC. The MICs in µmol/l of some compounds of the invention against a series of test organisms are listed by way of example in the table below.

Ex. No.	Staphylococcus aureus 133	Haemophilus influenzae Spain 7
2	15.63	7.81
4	15.63	31.25
6	7.81	15.63
9	7.81	62.5
48	0.98	15.63
109	0.98	62.5

Systemic infection with S. aureus 133

S. aureus 133 cells are cultured overnight in BH broth (Oxoid, New York, USA). The overnight culture is diluted 1:100 in fresh BH broth and spun at high speed for 3 hours. The bacteria in the logarithmic growth phase are centrifuged off and washed 2 × with buffered physiological saline solution. Subsequently a photometer (Dr. Lange model LP 2W, Berlin, Germany) is used to establish a cell suspension in saline solution with an extinction of 50 units. Following a dilution step (1:15) this suspension is mixed 1:1 with a 10% mucin suspension. 0.25 ml/20 g mouse of this infection solution is administered intraperitoneally. This corresponds to a cell count of approximately 1 × $10E^6$ organisms/mouse. The intraperitoneal or intravenous therapy is practiced 30 minutes following infection. Female CFW1 mice are used for the infection experiment. The survival of the animals is recorded over 6 days.

C) **Examples of pharmaceutical compositions**

The substances of the invention can be converted into pharmaceutical formulations as follows:

Tablet:

Composition:

100 mg of the compound from Example 1, 50 mg of lactose (monohydrate), 50 mg of corn starch, 10 mg of polyvinylpyrolidone (PVP 25) (BASF, Germany) and 2 mg of magnesium stearate.

Tablet weight 212 mg. Diameter 8 mm, radius of curvature 12 mm.

Production:

The mixture of the compound of Example 1, lactose and starch is granulated with a 5% strength solution (m/m) of the PVP in water. The granules are dried and then mixed with the magnesium stearate for 5 minutes. This mixture is compressed using a conventional tablet press (see above for tablet format).

Oral suspension:

Composition:

1000 mg of the compound from Example 1, 1000 mg of ethanol (96%), 400 mg of Rhodigel (xanthan gum) (FMC, USA) and 99 g of water.

10 ml of oral suspension correspond to a single dose of 100 mg of the compound of the invention.

Production:

The Rhodigel is suspended in ethanol and the compound of Example 1 is added to the suspension. The water is added with stirring. The mixture is stirred for about 6 h until the Rhodigel has finished swelling.

Solution for intravenous administration:

Composition:

100-200 mg of the compound from Example 1, 15 g of polyethylene glycol 400 and 250 g of injection-grade water.

Production:

The compound of Example 1 is dissolved together with polyethylene glycol 400 in the water, with stirring. The solution is subjected to sterile filtration (pore diameter 0.22 µm) and dispensed under aseptic conditions into heat-sterilized infusion bottles. These bottles are sealed with infusion stoppers and crimped caps.